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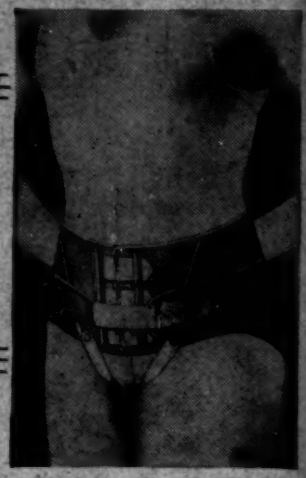

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 4 1954

SOME MEDICAL ASPECTS OF HUMAN CLIMATOLOGY IN THE EQUATORIAL TROPICS*

BY

F. P. ELLIS, O.B.E., M.D., M.R.C.P.

Surgeon Commander, Royal Navy; Lately Director of the Medical Research Council's Royal Naval Tropical Research Unit, University of Malaya, Singapore

Early in 1944 the Board of Admiralty invited the Medical Research Council's Royal Naval Personnel Research Committee to examine the effects imposed on ships' companies by the climatic conditions which were prevalent in warships operating in warm climates. At that time it appeared inevitable that the defeat of Japan would be accomplished only by a series of amphibious and air operations which would keep an enormous fleet supported by a train of supply and repair ships constantly at sea for many months, or even years, in tropical or subtropical waters. The impact of the warm climate on these operations could not be forecast, and it was clearly of the utmost importance to know more about it. The essence of the problem and the early activities of a subcommittee appointed to deal with it have been described by Critchley (1945, 1947), Bedford (1946), Ellis (1947, 1948, 1950), and Mackworth (1950). During the last five years this work has been continued at the Royal Naval Tropical Research Unit, Singapore. Some of the conclusions, which go a long way to provide a solution to the purely medical side of the wartime operational problem, have been referred to elsewhere (Ellis, 1953a).

I shall discuss three medical aspects of the warm-climate problem, with which the Singapore experiments were not primarily concerned but from which they could at no time be divorced—namely, skin diseases, fatigue, and heat incapacitation—and consider some of the general principles which underlie their prevention. In developing this theme I shall draw on the work of the Medical Research Council's team at Singapore and on numerous discussions with my colleagues Dr. R. K. Macpherson, Dr. J. S. Weiner, Mr. R. D. Pepler, Dr. J. O. Irwin, Dr. R. H. Fox, Miss H. M. Ferres, Mr. P. S. B. Newling, Mr. A. R. Lind, Dr. M. L. Thomson, Dr. P. J. Hare, Surgeon Lieutenant-Commander R. T. John, R.N., and Major J. M. Adam, R.A.M.C.

Skin Diseases

During the war about 10% of ships' companies in the Eastern and British Pacific Fleets and 6% of those on shore were treated every month for some form of skin disease. When the Tropical Research Unit advance party arrived at Singapore in 1948 an Army team, led by Major P. H. Sanderson, R.A.M.C., were just completing a dermatological survey of British troops in Malaya and Hong Kong. They found fungus infections on the bodies of one man in three, on the feet of one man in two, prickly heat affecting one in four, and 8% with bullous impetigo (Sanderson and Sloper, 1953). Prickly heat (miliaria rubra) and pyogenic and mycotic dermatoses were thus prominent in the initial appraisal of the difficulties to be surmounted in experiments which were to involve repeated daily work in warm atmospheres.

The precautions adopted were simple. No man with an infectious condition of the skin was allowed at first to work in the climatic chambers. Candidates with moderate or severe infections which were not easy to cure were rejected at their initial medical examination. Each subject wore freshly laundered shorts or overalls or worked in the nude each time he was exposed to high temperatures and was given two freshly laundered towels —one for use during an experiment and one for use afterwards. They used hot- and cold-water showers after each exposure. The bathrooms and climatic chambers (including personal furniture such as chairs and stepping-stools) were scrubbed out with disinfectant each Sunday morning. Each man wore his own plimsolls, a new pair being issued to him on arrival, except in experiments which involved heavy sweating on successive days, when they sometimes preferred to work in bare feet and were allowed to do so. The plimsolls were rinsed in fresh water and dried in a drying cupboard each night between experiments, so that the men always put on dry shoes.

On arrival at the unit approximately 35% of the subjects had mild mycotic infections, usually of the toe clefts, and were given the appropriate treatment. About 25% had mild acne vulgaris or boils or pimples. The latter were the only skin disorders which increased in incidence subsequently (to about 35%), and several men found that working in the heat made their acne worse also. Only 4% showed any evidence of prickly heat, and even then the diagnosis was sometimes doubtful. The rarity of this condition during the experiments illustrated that repeated exposure to very warm conditions for a few hours each day for as long as five months will not cause it, provided those exposed can spend some of the time between exposures in an atmosphere where their skin is not moistened with perspiration.

When the combined requirements of the Korean and Malayan campaigns threatened to curtail the supply of subjects during 1951 and 1952, confidence in these simple precautions was such that men were allowed occasionally to participate in experiments with quite severe dermatoses of fungal origin which were treated. No cross-infections were observed to occur, and the conditions were cured or improved during the experiments. During four years 320 men from the Royal Navy and the Army acted as subjects for periods varying from 2 to 201 days and were available at the unit for over 15,000 man-days. With one exception, which is described later, it was never

*A paper read at the annual meeting of the Services' Group of the Society of Medical Officers of Health on March 19, 1954.

necessary to remove a man from an experiment for skin disease. This justified a heavy laundry bill and the expenditure on installing adequate showers and a drying cupboard.

Clean bodies, clean clothes, clean and efficient bathrooms, routine inspections, and frequent and early treatment where necessary will do much to reduce the wastage of man-hours in areas where skin disease is rife. Under campaigning conditions all these ideals are often impossible to achieve, but they should be the aim of those responsible for the administration of ships, barracks, and permanent camps. The responsibility for maintaining acceptable standards of personal and barrack hygiene lies with the executive officers and non-commissioned officers, who are in intimate and continuous contact with the men, rather than with the medical branches, as antimalarial discipline did during the war; but unit medical officers can do much to inculcate the right ideas in these quarters. In ships, the best personal hygiene in the world cannot be expected to keep the skin healthy when the thermal environment is so warm that continuous sweating is unavoidable and the water, even from the "cold" showers, is so hot that a man can hardly stand under it. These evils can be avoided only by sound design and construction and by sending to the Tropics ships which have been built to operate in warm climates. This is now axiomatic following the dramatic reduction in skin diseases and other heat illnesses after the introduction of air-conditioning to submarines operating in the Tropics in wartime and more recently to frigates patrolling the Persian Gulf during the warm months of the year.

When the preventable skin diseases have been dealt with there will remain a small nucleus of conditions which cannot be cured and which get better only when the sufferer returns to a cooler climate, and for these invaliding is often the only solution.

Fatigue

Tropical neurasthenia (Eijkman, 1924; Carthew, 1927; Stannus, 1927; Castellani, 1929; Lamprell, 1948) and the syndrome to which the terms tropical fatigue or hot-climate fatigue have been applied more recently (Lee and Macpherson, 1948; Macpherson, 1949; Ellis, 1952a, 1953b) belong essentially to the same group of climatic disorders, but differ in degree and chronicity with the proportions of the climatic or neurotic components and the different circumstances under which they are encountered. When healthy men live for a long time in an unduly warm climate, some of them suffer from hot-climate fatigue, typified by lethargy, mental retardation, reduced powers of concentration and sense of responsibility, irritability, mild changes in personality, and forgetfulness. These are associated often with excessive sweating, unsatisfactory sleep, skin diseases, loss of weight and appetite, and ill-defined digestive disorders. This syndrome develops particularly when men live and work at levels of warmth which result in the presence of unevaporated sweat on the skin and in the clothing or bedding. The majority will suffer in one way or another after a time, but in a healthy community serious breakdown will not be encountered very often, and there may be little reference to the condition in routine sickness returns. Most of these effects can be surmounted temporarily when it is necessary to make a special effort, and are relieved by resumption of life in a cooler climate.

Factors other than climate, inertia, monotony, isolation, domestic stress, excessive social activity, adverse conditions of service, overwork, inadequate cultural influences, unsuitable clothing, insect pests, and ill-health may all colour the picture according to the local situation; but some of the features of "hot-climate fatigue" are nearly always present (Ellis, 1953b). The causes can be represented in various ways:

Hot climate alone (a warship's company in the Tropics).

Hot climate+inertia+domestic stress (housewife's fatigue).

Hot climate+monotony, perhaps+alcohol (as a result of long-term residence).

Hot climate+isolation+operational fatigue+domestic worries+insects+lowered morale (troops engaged in tropical warfare).

Hot climate+overwork+social stress, perhaps+alcohol (Government or Service officials in large centre).

Hot climate+monotony+domestic stress+isolation, perhaps+alcohol (a warship's company on detached service).

Hot climate+monotony+domestic stress+isolation+insects+cultural deficiencies (isolated tropical communities).

And the clinical picture can be as varied as the causes.

Some of the psychological characteristics have been investigated in the laboratory. At Cambridge, Mackworth (1950) used tests simulating various tasks which are carried out in warships, tanks, or aircraft to show that, even during exposures lasting only two to three hours, the performance of naval ratings and of men from the Royal Air Force deteriorates when the average effective temperature lies between 81 and 86° F. (27.2 and 30° C.).* At Singapore, Pepler observed a similar though more variable effect when the subjects were naval ratings who were acclimatized to the Tropics. This zone of warmth is only slightly above that—78–85° F. (25.6–29.4° C.)—within which the majority of sedentary lightly clad persons become uncomfortably warm in that part of the world (Ellis, 1952b, 1953c).

The complex, and only partially elucidated, physiological basis of fatigue in temperate climates may be complicated in warm climates by profuse sweating, with associated losses of water and electrolytes and the secondary effects on the skin and the circulatory systems, by the impact of a raised body temperature on cellular metabolism, the central nervous system, and neuromuscular conduction, and by the response to stress, when stress is present, of the endocrine system. A great deal has been learnt of the factors which give rise to fatigue in the Tropics, but we know very little of the physiological sequence which intervenes between the cause and the effect; although some pieces of this jigsaw puzzle are now beginning to fall into place.

Hot-climate Fatigue

We repeatedly saw acute fatigue developing at Singapore when 12 men were carrying out standardized work, stepping up on to and down from 12 in. (30 cm.) stools in time to a metronome, in a climate which was near to the limit they could tolerate. "Step-climbing" was always easy at the start of an experiment. They stepped uniformly in good time, and were fairly silent and circumspect. Perhaps 8 out of 12 would be reading magazines. As their exposure continued they started to sweat and some of them would stop reading. Then the step-climbing became "tired," although the time-keeping was still quite good. Next, some of the subjects would start stepping out of time, and this might consist either in stepping too quickly or stepping too slowly or stepping too quickly at one time and stepping too slowly at another. Their actions became badly co-ordinated; some staggered occasionally; some moved their arms very much more than they had done previously; some moved them less; a few looked as though they had the "weight of the world on their shoulders"; and one man would hyperventilate and grit his teeth. Euphoric cheerfulness and a smiling acceptance of the conditions would fluctuate with grumbling irritability and morose attitudes. Eventually, at times, some of them could not go on with their work. They did not collapse, but they simply could not continue to step on and off their stepping-stools and said that they felt so tired that they could fall asleep on the spot.

*Wet- and dry-bulb temperatures of 90 and 80, and 95 and 85° F. (32.2 and 26.7, and 35 and 29.4° C.) when the average air speed was 100 feet (30.5 metres) per minute and the subjects were stripped to the waist.

This excessive tiredness was accompanied sometimes by nausea, headache, light-headedness, or aches in the legs or trunk, but it also occurred alone. Slowness in answering questions, mistakes in reading a clock or in naming a colleague or messmate, a false appreciation of the passage of time, over-confidence in their ability to survive, and afterwards a poor memory for events at the time simulated the symptoms of anoxia. These latter features may occur a considerable time before an individual finds the atmosphere intolerable. They are insidious, often unrecognized by the person affected, and, if he should be an operator who needs to think and act quickly, may have disastrous effects on the efficiency with which he does his job. The identical work which the men were doing was tolerated easily under slightly cooler conditions, and "acute hot-climate fatigue" seemed as useful a term for describing this condition as any other.

Neither hot-climate fatigue nor tropical fatigue is an entirely satisfactory descriptive term for the more chronic effects of warm climates, and both are likely to be abused. A phrase indicating a general slowing down and inefficiency, but not implying that the condition is due to either fatigue or neurosis, such as "hot-climate decrement," might be more acceptable; but it is wise to pause before coining any more new names for this diffuse group of conditions. It certainly does not help the recovery of a man with a good personality who is suffering from severe environmental stress to label him a neurasthenic; nor does it help, at times, to send him to a psychiatrist when all he wants is a rest in cooler surroundings. "Tropical neurasthenia" should be reserved as a diagnosis for the more serious and much rarer cases with well-developed neuroses or psychoses, which tropical environmental stress may precipitate in persons who are already unstable or who have been ill before.

Heat Incapacitation

Probably the most important wartime sidelights on the aetiology of heat incapacitation were the recognition that widespread dermal anhidrosis following prickly heat might aggravate fatigue (Wolkin, Goodman, and Kelley, 1944; O'Brien, 1947) or precipitate acute heat incapacitation (Ladell, Waterlow, and Hudson, 1944), and the frequent observation that salt deficiency might give rise to fatigue as well as cause heat cramps or collapse.

The incidence of heat incapacitation is not easy to gauge. Many cases never come under medical care, or the symptoms are so transient that even if they do they are not included in the official sickness returns or are attributed to some other cause. Reports from ships' medical officers when the Eastern Fleet was congregating in 1944 revealed that the actual cases diagnosed as heat exhaustion amounted to about 5% of the total strength per year (0.4 per 100 man-months; Ellis, 1948). The true incidence must have been very much greater than this. In an excellent review of 120 naval patients with diagnosed salt-deficiency states, observed during two and a half years afloat in the Tropics, Stenning (1945) commented, "It is doubtful whether any single member of the ship's company who served at sea in the Tropics for more than six months was not affected to a greater or lesser extent by the effects of uncompensated salt loss." He divided his cases into subclinical salt deficiency, heat shock, heat exhaustion with abdominal pain, heat cramp, the "dyspeptic type," the "vomiting type," the "vomiting-diarrhoea-pyrexial type," salt deficiency with low-grade pyrexia, and hyperpyrexia. Loss of salt from the body, an abnormally low concentration of salt in the urine, and a satisfactory therapeutic response to salt administration were always diagnostic features.

Further evidence was provided by Thomson (1946), who described 66 cases which occurred in a battleship in the Eastern Fleet between January, 1944, and March, 1945: 89% were due to primary salt deficiency. Similar accounts are to be found in other naval medical officers' journals and leave no doubt that in wartime these problems were of major importance to the Navy. Notable features were the rarity of true hyperpyrexia—that is, temperatures exceeding 104° F. (40° C.)—and that newcomers to the Tropics were affected more frequently than acclimatized personnel.

In peacetime, ships are not usually manned with their war complements, nor are they closed down for action for long periods or "darkened" at night. Fuel economies limit the amount of sea time and high-speed steaming which is possible. These factors all help to alleviate the thermal environment between-decks. A request from the Commander-in-Chief of the Far East Station for all cases of heat exhaustion to be reported between June, 1952, and February, 1953, drew no replies. Minor heat incapacitation is not quite so uncommon as this suggests, particularly in troopers and other ships passing through the Tropics; but it is usually recognized promptly, and those afflicted recover rapidly and are often well again by the time they are seen by a medical officer.

The incidence of heat exhaustion was said to be as low in Army units as it was in Naval units in Malaya. However, my colleague, Captain R. H. Fox, R.A.M.C., kept this possibility in mind when he went on a three-day anti-bandit patrol in a fresh-water swamp during the rainy season whilst he was on leave in 1952. Although they were shaded from the sun by the jungle, the relative humidity of the atmosphere was high, and this, together with the heavy work of ploughing through swampy undergrowth whilst carrying heavy equipment, caused excessive sweating. It was considered that under these conditions casualties due to water and salt deficiency might occur, especially since drinking unpurified swamp water was discouraged, all fresh water had to be carried, and the men did not appreciate fully the necessity to drink adequately at frequent intervals. There were no casualties in his platoon, although the strain was severe, but four men in another platoon were incapacitated during the same operation and dropped out at various times, thus hazarding themselves and the rest of the party. Salt-deficiency dehydration was by far the most likely cause of their failure.

After discussions with Captain Fox, Lieutenant-Colonel W. M. Stewart, R.A.M.C., inquired concerning the incidence of similar cases amongst other units in the area. He concluded from the replies that in general the medical officers to the operational groups were not willing to diagnose heat exhaustion unless there was some severe disability without any other obvious diagnosis; but 31 cases of heat incapacitation were reported by the medical officer of one battalion within three months. These were all confirmed to be due to salt deficiency by the absence of chlorides in the urine and a favourable response to treatment with salt tablets. It is highly probable that the true incidence of heat incapacitation in the Army and in the Navy was, and still is, masked by the transient nature of this condition when it occurs in healthy men.

Physiological Features of Heat Incapacitation

Now, the subjects of the Singapore experiments were acclimatized to work in a warm climate, supplied plentifully with palatable drinking-water, and encouraged to take salt either in accordance with their personal wishes or as a fairly accurate replacement of the salt they had lost by sweating. Under these circumstances very few developed heat cramps. It was a rare occurrence for a man to collapse so completely that he lost consciousness while working in the climatic chambers, although they had to be supported frequently when they retired and afterwards were amnesic, either partially or completely, for the events at the time. True hyperpyrexia was never seen. Why, then, were they incapacitated?

First, there were the thermogenic factors, the heat absorbed from the air by conduction and convection and by the electro-magnetic waves of radiant warmth from the surroundings, and the heat generated internally by their metabolic processes. Together, these raised their temperatures beyond the limits at which their bodies could function efficiently.

Second, there were the processes which permitted evaporative cooling of the skin surface to take place under favourable circumstances but led to deficits in the body water and salt. These deficits occurred even when water was freely available and the men were trying their best to drink it, for many men cannot absorb water from the alimentary tract rapidly enough to maintain their body water at a constant level when they are sweating profusely. If they try to drink more than their body is willing to accept the water distends their stomachs, causing nausea, distaste for water, and, not infrequently, vomiting, when 1 to 2 pints (570 to 1,140 ml.) of fluid are projected forcibly. This distension of the stomach alone appeared to precipitate syncopal symptoms sometimes, presumably by pressure on the great veins, for the symptoms were relieved in some measure after vomiting. The loss of water in pure water deficiency is usually borne by the total fluids of the body, but when deficiency of sodium chloride is associated with it, as it is when sweating is the main cause, the strain will tend to fall more on the small extracellular fluid compartment, which includes the important plasma water. A relatively small deficit under these circumstances may give rise to symptoms of circulatory failure if the rate of sweating is high.

Third, vasovagal faintness, probably due to a sudden lowering of blood pressure in the great veins returning blood to the heart caused by a reduced circulating blood volume, the gravitational effects of sudden changes in posture, sudden peripheral vasodilatation or acute gastric distension, or due to emotional apprehension of the heat, was a not uncommon cause of temporary heat incapacitation. This was seen when subjects who had been sweating freely rose from a sitting to a standing position after they had been resting, or even when they sat upright after lying back in a canvas chair; and at times it would suddenly precipitate incapacitating symptoms in a man who had been symptom-free. Slowing of the heart rate was a characteristic feature, despite the climatic stress, as it is in the syncope of blood donors. Emotional factors may have contributed to the sudden exit of some subjects from experiments where climates of great severity were used; but they were more clearly demonstrated by occasional visitors who thought they were going to faint within a few minutes of entering the climatic chambers before any other effect could be incriminated, rather like medical students seeing their first operation.

Fourth, as I have described already, even though the thermogenic influences did not appear to be in themselves overpowering, although the intake of salt and water seemed ample and they did not faint, there were occasions when men simply could not continue with work which they could do with ease in a cooler climate. This accentuation, under very warm climatic conditions, of the normal fatiguing effect of a given work situation may of course be secondary to the combined effects of minor degrees of dehydration, pyrexia, or circulatory insufficiency, or to metabolic or endocrinological changes which have not yet been identified in relation to fatigue, or it may be a primary effect of the climate on the mechanism of fatigue itself.

This sequence of events can be related to the more severe clinical conditions which occur when quick relief from a warm environment is not possible, when the thermogenic load is greatly increased by powerful external factors such as the heat of the desert sun, heavy work, or impermeable clothing, when the normal compensatory mechanisms are interfered with by reduced sweating from acquired or congenital defects of the sweat glands, or when salt deficiency and dehydration are unrecognized or cannot be corrected. It provides a useful basis for classifying the mechanisms responsible for heat incapacitation when considering prevention and treatment.

Physiological Features of Heat Incapacitation in Healthy Young Men

I. *Water and salt deficiency* (cramps, headache, circulatory failure, alimentary tract disorders, syncope, and fatigue)

II. *Thermoregulatory failure* (rapidly rising body temperature, perhaps with headache, vomiting and clouding mentality, with either a dry or moist skin)
- (*a*) Thermogenic (due to excessive warmth, hard work, too much clothing, etc.)
- (*b*) Anhidrotic: acquired (following miliaria rubra or sunburn); congenital (congenital sweat-gland defects)
- (*c*) Toxic-infective (for example, malaria and infectious fevers)

III. *Circulatory failure* (rapid pulse, falling B.P. and dizziness, or "blackout" with bradycardia)
- (*a*) Intense peripheral vascular dilatation
- (*b*) Pooling of blood in dependent extremities
- (*c*) Reduced circulating blood volume
- (*d*) Acute distension of the stomach
- (*e*) Vasovagal syncope due to reduced pressure in great veins, or, sometimes, emotional factors

IV. *Acute fatigue* (inability to work efficiently in the relative absence of I, II, and III)

Heat incapacitation is a clumsy diagnosis; but a better alternative, for describing a condition in which fatigue, collapse, cramps, vasovagal fainting, abdominal upsets, or pyrexia may all be presenting symptoms of similar underlying physiological changes which prevent a man doing his work in a warm atmosphere, does not come easily to mind.

A review in retrospect of 110 case histories of acclimatized fit young men who were unable to complete their experimental tasks at Singapore revealed that fluid and electrolyte loss, pyrexia, and frequently circulatory failure too, often occurred together. One of the most common early complaints was abdominal discomfort with nausea, and another was headache. Cramps were a prominent feature only four times, and rectal temperatures rose above 104° F. (40° C.) on only three occasions. Postural fainting, probably vasovagal and associated with transient bradycardia, was a relatively common terminal incident, and severe progressive fatigue was another. One man sweated so profusely that his rectal temperature rarely reached 101° F. (38.3° C.), but he succumbed to circulatory failure unless he maintained a steady fluid intake. Another who sweated less profusely than most of the others, and was often unable to drink enough to replace the amount he did sweat, would depart before the others with a rapidly rising rectal temperature (103° F. (39.4° C.) or higher); but there was nothing to suggest that we were dealing with more than one clinical entity despite the diverse physiological effects and symptomatology.

None of the men exhibited dermal anhidrosis; but one of them, who became suddenly less heat-tolerant than he had been previously, developed diffuse and generalized miliaria profunda, "rice-grain" distensions of the sweat glands, when he worked in a hot atmosphere. These became more prominent as he approached the limit of his endurance and faded within 10 minutes when he recovered afterwards in a cooler place. They were associated with marked acne vulgaris of the face, but not elsewhere. No obvious histological abnormalities of the sweat glands were detectable in biopsy material recovered from miliaria-bearing areas. It was thought to be a constitutional defect related possibly to androgen–oestrogen imbalance.

The less acute states which do not lead to complete incapacitation and account for more chronic climatic illness may be classified in the same way. But there can be no strict demarcation between acute and subacute heat illness, nor between heat incapacitation which is due purely and simply to failure to adjust physiologically to a strenuous environment and failure which is aggravated by concomitant somatic or psychological defects. The scheme shown is not fully comprehensive, but it is adequate to cover the more common warm-climate effects which are encountered in healthy young adults. The prophylaxis of these conditions includes the prevention of skin diseases, which has already been discussed, the provision and use of adequate amounts of drinking-water and salt, and the control of the thermal environment.

Salt and Water Requirements

In the United Kingdom most adults who are not employed in hot industries have a total daily water intake or output of about 2.5 litres, and their salt requirements are met by the salt in their food or taken on the plate. Sweat contains between 0.1 and 0.6% sodium chloride, and the

amount a man sweats is related to the stress imposed by the thermal environment and the average energy cost of the work he is doing. Thus in one Singapore experiment, when a man (weighing 72 kg.) sat at rest for only three and a half hours wearing a pair of shorts in a saturated atmosphere at the temperature of the body—99.4° F. (37.4° C.), relative humidity 97%—he sweated 6.2 litres of sweat, an amount approximately equal to his total circulating blood volume or his normal water output for two and a half days in England. If the average salt concentration of his sweat had been 0.3%, he would thus have lost 18.6 g. in this short period of time.

When we began work in Singapore we accepted the advice that provided a man was allowed to drink as much water as he wished and advised to take plenty of salt with his food he would not become dehydrated. But when this advice was followed in an experiment involving continuous daily exposure (for four hours) for several months there was clinical and physiological evidence that some subjects became dehydrated and less heat-tolerant. When the salt losses were replaced systematically on a later occasion by giving each man 1 g. of salt for each litre of sweat he secreted during an experiment as well as by encouraging the practice of taking salt with the food, the men were able to withstand repeated daily exposure to much higher temperatures with equanimity.

Individuals vary enormously. Under the same working conditions one man may lose twice as much sweat or three times as much salt per unit of body weight as another man, and the day-to-day losses of the same individual over a period of several months may vary nearly as much. Furthermore, identical environmental conditions rarely recur outside the laboratory.

From the evidence available, salt appears to be the only substance which leaks away during heavy sweating in amounts which the body cannot afford to lose. Other electrolytes and most of the water-soluble vitamins are present, but in amounts which are unlikely to cause deficiencies in normally nourished people in the Tropics (Lugg and Ellis, 1954). Limitations of technique have left our knowledge of this aspect incomplete, however, and the sweat should not be overlooked as a possible pathway by which tropical deficiencies may occur until these gaps have been filled.

In practice the usual finding is that those who cannot avoid sweating freely day after day regulate their salt and water requirements without supervision, provided salt and palatable drinking-water are available and they understand the nature of salt deficiency. Many men who cannot take free salt can take sugar- and enteric-coated salt tablets. They learn that if they have diarrhoea, a poor appetite, vague indigestion, and develop a blotchy skin after taking a liberal supply of salt, then they have probably taken too much; and, alternatively, if they lose their appetite and energy and experience headaches, cramp-like aches and pains, occasional dizziness, "black-outs," and perhaps some loss of weight, when they have been sweating profusely and neglecting their salt intake, they recognize that this is probably the reason. The prompt therapeutic response in either case will show if they are correct in their assumptions.

Many men who cannot, or will not, drink tepid water will welcome cooled water. The way in which a fixed water ration is used may also influence the benefit to be derived from it. Recent observations by Kenney (1954) on male West Africans working in a warm atmosphere showed that when they drank more than 100 ml. of water in one dose a significant diuresis offset rehydration, so that when a man drank the same water ration in frequent small doses instead of occasional larger doses he saved as much as 300–400 ml. in 90 minutes.

General measures, such as increasing the salt content of food or drinking-water, need to be handled cautiously in view of the wide variation in individual requirements and likes and dislikes. In warships salting the main water supply is not practicable because of the adverse effect on the ships' water-pipes. But the salt content of bread has recently been increased successfully on the Far East Station. The daily intake of the average man was increased by approximately 5 g.* in this way without impairing the palatability of the bread.

General directives concerning salt and water requirements in tropical theatres should be available and be kept up to date with current opinion on these matters; but their recommendations should be interpreted with due regard to the wide range of human variability and to the fact that too much salt, as well as too little, gives rise to unpleasant symptoms. The requirements under different operational circumstances can be assessed satisfactorily only by those on the spot. Further accurate studies of the salt and water requirements of men serving under different campaigning and climatic conditions would be of great practical value.

The Control of the Thermal Environment

It is not the duty of a health service to recommend measures for the control of the thermal environment, but it is a medical responsibility to advise on the limiting conditions above which adverse effects on efficiency, health, or comfort are likely to occur. A provisional recommendation made by the Royal Naval Personnel Research Committee to the Admiralty 10 years ago, that, wherever practicable, in spaces where men live or work in ships the effective temperature (or corrected effective temperature) should be kept below 80° F. (26.7° C.) and should not exceed 86° F. (30° C.) (Bedford, 1946), is supported by the results of the Singapore experiments as well as any such general recommendation could be expected to be. But I would prefer to see 78° F. (25.6° C.) as the upper desirable limit rather than 80° F. (26.7° C.). If the ventilation and air-cooling arrangements of ships, armoured fighting vehicles, or aircraft built for warm climates impose warmer conditions than 86° F. (30° C.) effective temperature on Service personnel for more than short periods the efficiency of the machine will be offset by the inefficiency of the crews, and the more this limit is exceeded the more serious the human failure is likely to be. There is no reason to believe that similar considerations do not apply to commercial enterprises and shipping.

The Singapore studies emphasize that when men are working in warm environments which are near to the limits they can tolerate, very small additions to climatic stress may turn a tolerable situation into one which few can withstand. One cannot add to the vigour of their work, expect them to wear extra clothing or equipment, introduce additional heat-producing machines into the compartments in which they work, increase the numbers of sweating and heat-producing occupants, or reduce the supply of ventilating air and air movement with impunity, or this narrow margin may be exceeded. A rise in wet-bulb temperature of only about 2° F. (1.1° C.) or a relatively small decrease in air movement, from a pleasantly perceptible (150 ft./min.) to a "still" or stagnant condition (20 ft./min., a normal indoor condition in England, or less) are sufficient to change otherwise identical and acceptable conditions of climate, work, and clothing into conditions which none can tolerate. Conditions which can be tolerated for two hours cannot be endured for a third hour. A man who sits at rest for three to four hours can withstand a wet-bulb temperature 4 to 5° F. (2.2 to 2.8° C.) higher than if he engages in constant light activity or intermittent work which is rather more strenuous.

When men who have been stripped to the waist wear drill overall suits over their shorts in very warm climates the additional stress is similar to that imposed by increasing the mean radiant temperature of their surroundings by about 40° F. (22.2° C.). Under these conditions the suit does not help them to withstand long-wavelength heat radiations such as men may have to endure in ships' machinery spaces. The waves of radiant warmth are impeded by the suit, but evaporative cooling is reduced so considerably that this gain

*The salt content of bread baked to the revised naval recipe is 10 g. per lb. (22 g. per kg.), compared with 5 g. per lb. (11 g. per kg.) with the normal recipe.

is discounted, and the overalls absorb approximately their own weight of sweat. The very real protection which overalls provide against steam leaks, burns from very hot metal parts, dirt or oil, and flash burns in wartime cannot be denied; but they should be made of the lightest and most ventile and durable fabrics which will meet these other requirements.

Since Bedford (1946) proposed that the effective temperature scales should be used in the Navy for describing warm environments, no better alternative has appeared. The ventilated dry- and wet-bulb thermometers, of either the "sling" or Assmann design, still provide the medical observer with the most accurate and convenient method for measuring the air temperature and humidity. The silvered katathermometer has not been replaced by any more simple and equally accurate alternative for measuring turbulent air currents of low velocity. The globe thermometer has emerged successfully from a series of comparisons, with other available methods for determining the mean radiant temperature, made by Newling in a "radiant-heat tunnel" at Singapore. The "corrected effective temperature" also gained support from physiological investigations by Macpherson and others of the team in the same radiant-heat tunnel (Macpherson, 1952). But it is wise to remember that the effective temperature scales were constructed primarily to deal with the thermal environment to which persons engaged in light work are exposed indoors during the summer in homes and offices in North America. They are most useful when used for this type of environment, and are beset with pitfalls when used for situations which they were not designed to meet.

Conclusions

Apart from information about the various factors which limit work at high temperatures, probably the most useful facts which have been derived from these studies so far are, first, that the effects on men in the Tropics are very similar to the effects observed on men doing the same kind of work in temperate climates, provided the workers are trained to work in the heat and are able to recuperate between exposures in an atmosphere which is not so warm that it induces perceptible sweating; secondly, that the upper tolerable levels of warmth for men in a similar state of training for work in warm atmospheres are much the same whether they are living in the Tropics or in England; and, thirdly, that the variations between individuals, and even in the same individual from day to day, are very great at times. Observations made on small numbers, or on only a few occasions, may be misleading if they are used as a basis for general conclusions. Finally, with regard to men who are not specially trained to work at high temperatures, Weiner and Macpherson (1953) have produced evidence, from experiments carried out under otherwise identical conditions in Singapore and at Oxford, which indicates that untrained men in England are less heat-tolerant than untrained men in Singapore.

I have referred to only a few aspects of the many problems which arise from the impact of warm climates on man, and no attempt has been made to review contemporary opinion on these controversial topics. There is still much to be learnt. Special situations, such as those which result when men have to work hard and wear impermeable protective clothing in warm atmospheres, may need to be investigated as separate problems when they arise, and the effects of repeated and prolonged exposure to warm atmospheres require much more study. But, within the limitations of the techniques available at the present time, many of the principles which are relevant to the practical problem of maintaining the efficiency and health of men engaged in military or naval operations in warm humid climates are now established as firmly as they are likely to be by a purely experimental approach, and should be tested thoroughly in practice. In this way the shortcomings of the results of research will be revealed and new problems will be uncovered.

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COMA AND ALLIED DISTURBANCES OF CONSCIOUSNESS IN HYPOPITUITARISM

BY

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In an early account of hypopituitarism Simmonds (1914) described a woman who was subject to attacks of unconsciousness, one of which ended in death. Later it came to be recognized that these patients were prone to loss of consciousness and often died in coma, a phenomenon which was usually attributed to hypoglycaemia. Further experience has shown, however, that hypoglycaemia is only one of many factors which may affect their state of consciousness. Allott and Simmons (1951) and Summers and Sheehan (1951) have discussed "hypopituitary coma" in post-partum necrosis of the pituitary gland, while Caughey *et al.* (1952) and Ingraham *et al.* (1952) have reported on coma with tumours in and around the pituitary fossa. In other papers Caughey (1953, 1954) has described a variety of factors causing disturbances of consciousness in hypopituitarism. These changes of consciousness included hypersomnia, fainting, hypoglycaemic attacks, and "hypopituitary coma." From these and other reports it is clear that these patients are unduly vulnerable to factors affecting the level of consciousness, and that the diagnosis and

correction of the resulting coma require recognition as a medical emergency. Now that measures are at hand which will protect these patients against many of the effects of surgery, infection, and other stresses, and in the light of more recent experience, we feel justified in presenting a further report.

This report is based on 17 cases of hypopituitarism. All the patients showed disturbances of consciousness, which varied in severity from mild confusion, hypersomnia, and defective cerebration to stupor and profound coma. The immediate precipitating factors were numerous, and included operations in the vicinity of the pituitary fossa, pituitary apoplexy, infections, hypoglycaemia, drugs and anaesthetics, electrolyte disturbances, water intoxication, and cerebral anoxia. Ten of these cases have been fully described already (Caughey, 1954) and are not recapitulated here in any detail; the remainder are reported more fully. The endocrine findings in all these cases are summarized in the Table. As a result of further experience the material is presented in a different form from that used in the earlier report. Examples are given to illustrate coma arising from the various precipitating causes. Then the aetiological factors and, finally, diagnosis, prevention, and treatment of hypopituitary coma, are discussed.

Factors Which May Precipitate Changes in Consciousness

1. Surgery of the Pituitary Gland

After operations on pituitary tumours there is a risk of coma which may prove fatal. In Grant's (1948) series of 71 cases of pituitary adenomata, three patients died in post-operative coma which lasted from five to twelve days. Before operation their basal metabolic rates were less than −30%, and at necropsy there was atrophy of the gonads and of the adrenal and thyroid glands. Of Grant's 30 patients with craniopharyngioma, 10 died shortly after operation, several in coma and with manifest polyglandular hypoplasia. Grant believed that there was a higher operative mortality when endocrine function was defective, and advised caution before proceeding with surgical exploration.

We have seen prolonged coma follow intracranial operation in four patients with pituitary tumours (Cases J. P., S. M., J. H., and K. M.). All had hypogonadism, but in only two was there clear evidence of adrenal or thyroid failure. We have also seen a similar type of coma following operation on a pituitary eosinophil adenoma in a patient with acromegaly, but with minimal evidence of hypopituitarism (Caughey, 1954). After operation these patients failed to regain consciousness and remained stuporous, or comatose, for several days, one for as long as six weeks, before recovering. The clinical findings were remarkably uniform. The patients lay quiet and incontinent, but could just be roused by painful stimuli. Primitive reflexes, such as grasping and sucking, could not be elicited. They all recovered and showed complete amnesia for the period of coma. Pulse rate and blood pressure were normal or only slightly lowered. The temperature was raised in one, normal in three, and low in one. Blood-sugar levels were normal, and in only one was there a low plasma sodium concentration. The following is an illustrative case.

J. H., an architect builder aged 46, had developed a bitemporal hemianopia over the course of four years, and for three years had had left frontal headaches. His skin had always been soft and bodily and sexual hair growth scanty. On examination he was well nourished but sallow, with a wrinkled face. Facial and pubic hairs were scanty and axillary hair was absent. Both optic disks were pale and the pituitary fossa was enlarged. Adrenal function was found to be defective (see Table). After an intracapsular removal of a chromophobe adenoma, he became semi-comatose and was doubly incontinent. He was twice re-explored, confirming the absence of haemorrhage at the operative site. Three days after the second operation the blood pressure was 100/70 mm. Hg and the plasma sodium and potassium 129 and 5.5 mEq respectively per litre, and the blood sugar 120 mg. per 100 ml. Cortisone (intramuscular) and phenylephrine were given on the fourth post-operative day, and consciousness returned two days later, with amnesia for the period of stupor.

2. Pituitary Apoplexy

So-called pituitary apoplexy is a rare syndrome caused by haemorrhage into a pituitary adenoma. Aitken and Russell (1934) described such a case in a man aged 50 with hypopituitarism. A few hours after the onset of dizziness, weakness, and vomiting he became semiconscious and remained so for three days. On recovery he was found to have become blind in the left eye, and he remained lethargic until 41 weeks later, when he died in his sleep. At necropsy there was a chromophobe adenoma of the pituitary gland associated with an intrasellar haemorrhage, and the testes and adrenal and thyroid glands were found to be atrophied.

The following case also illustrates this further cause of coma.

Endocrine Function in 17 Cases of Hypopituitarism Subject to Coma or Allied Disturbances of Consciousness

	Case	Age	Sex	Adrenal Function: Gonadal Function: Clinical Hypogonadism	Adrenal Function: Gonadal Function: 17-Ketosteroid Excretion mg./24 Hrs.	Adrenal Function: Increased Insulin Sensitivity	Adrenal Function: Impaired Water Diuresis	Thyroid Function: E.C.G. Voltage	Thyroid Function: B.M.R. %	Thyroid Function: Plasma Cholesterol mg./100 ml.	Thyroid Function: I^{131} Uptake	Thyroid Function: Clinical Myxoedema	Additional Features
Post-partum pituitary necrosis*	G. ..	50	F	Yes	—	—	—	—	—	420	Normal	Yes	
	J. T. ..	57	F	,,	0·5	Yes	—	—	−10	—	—	,,	
	G. G. ..	36	F	,,	1·1	—	Yes	—	—	220	—	,,	
	McK.‡	53	F	,,	0	Yes	,,	—	—	410	—	,,	
	McL.	46	F	,,	—	No	—	—	−21	—	—	,,	
	J. B. ..	53	F	,,	0·9	Yes	Yes	Low	−48	297	Subnormal	,,	
	I. F. ..	54	F	,,	—	,,	,,	,,	−37	396	,,	,,	
	E. K.	52	F	,,	0·6	,,	,,	,,	−24	448	,,	No	Diab. mellitus (modified)
	D. B.‡	24	F	,,	—	—	—	—	—	—	—	,,	
Cranio-pharyngioma	H. B.	74	M	,,	3·1	Yes	—	—	−22	260	—	,,	
	J. D. ..	52	M	,,	9·5	,,	—	—	—	—	—	,,	Dwarfism
	J. P.† ..	44	M	,,	—	—	—	—	—	—	—	,,	
	I. K. ..	63	M	,,	5·0	Yes	Yes	Low	−7	170	—	,,	
Pituitary adenoma	S. M.†	47	M	,,	0·5	,,	—	—	—	295	—	,,	
	J. H.†	46	M	,,	0·3	,,	—	—	—	304	—	Yes	
	K. M.†	36	F	,,	4·3, 7·5	No	Slight	Normal	−18	—	Normal	No	
	L. S.‡	47	M	,,	1·4, 1·9	Yes	Yes	Low	+3, +4	187	,,	,,	

* All gave a history of failure of lactation and amenorrhoea following severe post-partum haemorrhage or sepsis.
† Pituitary tumour verified at operation.
‡ Diagnosis verified at necropsy, which also revealed hypoplasia of the adrenal cortex.

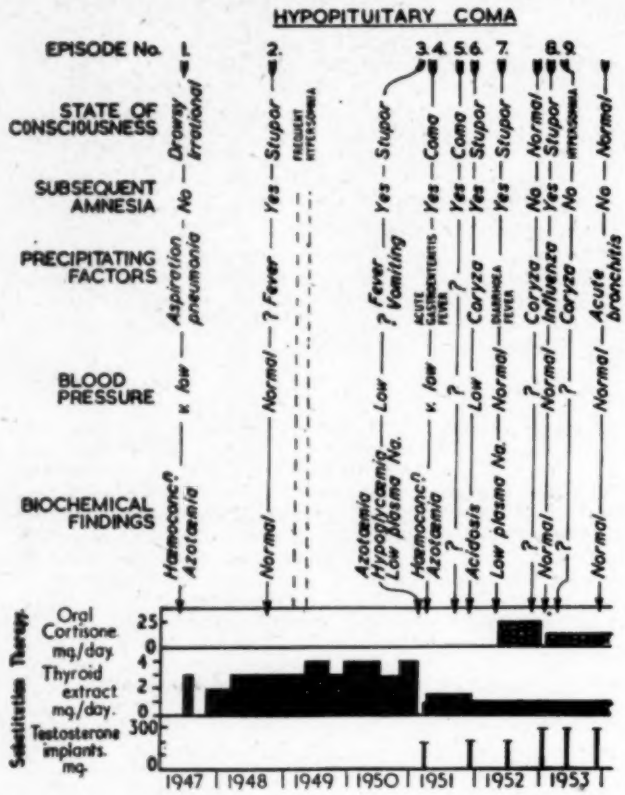

FIG. 1.—Hypopituitary coma in relation to replacement therapy in Case I. F. The comatose attacks were not prevented by regular therapy with thyroid extract and testosterone implants. During two years of regular cortisone therapy there has been only one attack of hypopituitary coma, which occurred during influenza contracted 10 days after stopping cortisone. During episode 9 (mild hypersomnia during coryza) the daily dose of cortisone remained at 12.5 mg.

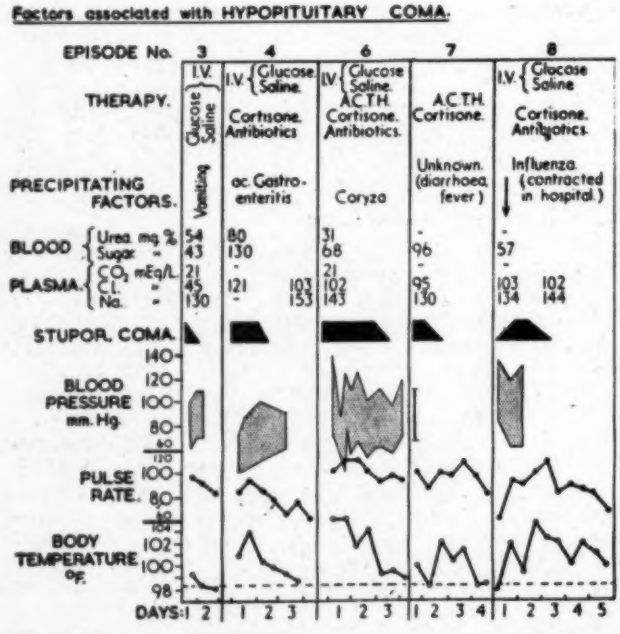

FIG. 2.—Clinical and biochemical findings during attacks of hypopituitary coma in Case I. F. Five of the episodes tabulated in Fig. 1 are shown in greater detail. Of the clinical and biochemical findings, the only factor common to all the episodes was pyrexia.

L. S., a painter aged 47, was admitted to another hospital, unconscious, in May, 1954. In August, 1950, he was found to have hypopituitarism, due to a chromophobe adenoma of the pituitary gland. There was failure of gonadal and adrenal function, but thyroid function was normal. After a year of testosterone therapy he refused further treatment.

On the day of his final admission he was found semiconscious and incontinent of faeces, having been well the previous day. On examination he was stuporous and febrile—temperature 103° F. (39.4° C.)—with a blood pressure of 108/60. Neurological examination was then negative. The following day he became irritable and could not be roused; the plantar responses were now extensor, and the right pupil was small and reacted poorly to light. Lumbar puncture yielded a clear fluid with normal pressure. That evening he died. Necropsy (Dr. S. Robinson) showed an unruptured unilocular cyst, 3 cm. in diameter, full of blood-stained fluid, bulging from the pituitary fossa into the base of the brain, and arising from a chromophobe adenoma. The brain was oedematous, with flattened convolutions and ablation of the lateral ventricles. There was moderately severe adrenal and testicular atrophy, but the thyroid gland was essentially normal.

The coma in this case was probably due to acute haemorrhage into a cystic chromophobe adenoma in a patient with hypopituitarism.

3. Infections

Patients with hypopituitarism usually sleep well and for long periods. Infections often aggravate their hypersomnia and may cause mental confusion or coma (Wilson, 1953; Caughey, 1954; Peters *et al.*, 1954).

One of our patients stated that during influenza and other fevers she would sleep for 48 hours without waking to take food. Another (J. D.) slept for two days during an attack of influenza. Infections, such as colds, influenza, or gastro-enteritis, caused drowsiness, confusion, and eventually coma in eight of our patients, as illustrated by the following two cases:

I. F., a widow now aged 54, was first admitted to hospital in 1947 with severe hypopituitarism. In 1925 her fourth pregnancy had ended with a post-partum haemorrhage and puerperal fever, and was followed by scanty and infrequent menses. After a fifth pregnancy in 1927 there was loss of libido, and her menses ceased at the age of 36 (1936). Since 1940 she had gained weight, and since 1945 had noticed dryness and puffiness of her skin and thinning of her scalp and superciliary hair. She became constipated and intolerant of the cold and complained of being "muddle-headed" and always drowsy. On examination she looked myxoedematous. The axillary hair was absent and the pubic hair scanty. The blood pressure was 120/80 mm. Hg with a pulse rate of 56. Hypopituitarism was confirmed (see Table) and on admission haemoglobin was 65%, blood urea 38 mg. per 100 ml., and plasma chlorides 107 mEq per litre.

A week later she developed a pneumonic lesion and became febrile, and at times stuporous. Several features such as hypotension (90/65), haemoconcentration (haemoglobin rose to 90%; plasma chloride 117 mEq per litre), and azotaemia (blood urea 136 mg. per 100 ml.) were suggestive of an adrenal crisis. She responded incompletely to antibiotics and intravenous saline, and remained in a fluctuating state of hypotension (blood pressure 65–100/40–70), with nausea, vomiting, hypochloraemia (plasma chloride 90 mEq per litre) and acidosis (plasma CO_2, 17.8 mEq per litre) for three months. During this period the administration of thyroid, 3 gr. (0.2 g.), daily and "eucortone" (10 ml.) on alternate days made little difference to her clinical course. Subsequent Cutler tests aggravated her hypotension but caused little chloride depletion. Her progress in relation to therapy over the next seven years is summarized diagrammatically in Fig. 1. After a period of comparative well-being on thyroid extract alone, she suffered many attacks of stupor and coma, mostly precipitated by gastro-enteritis or acute infections of the upper respiratory tract, and all accompanied by fever. Continued thyroid extract, with the addition later of testosterone implants, did not lessen the frequency of the comatose attacks. The clinical and biochemical findings at the onset of coma were very variable (Fig. 2); hypoglycaemia was present only once. Since taking cortisone, 12.5 to 25 mg. a day, she has been free from coma for two years, despite repeated infections; the only exception being when she caught influenza after discontinuing therapy for 10 days.

The following case is of exceptional interest in that fatal coma during acute pyelonephritis occurred within three

months of a severe post-partum haemorrhage, pituitary necrosis being confirmed at necropsy.

D. B., a housewife aged 24, was admitted to hospital unconscious in April, 1949. During the week before admission she had complained of frequency of micturition and backache, and on the morning of admission she had become comatose and incontinent. Three months previously her fourth pregnancy had ended with a post-partum haemorrhage (systolic blood pressure 60 mm. Hg, haemoglobin 32%), treated some hours later by blood transfusion. Subsequently she had failed to lactate and had become languid, anorexic, and unable to perform her usual household duties. On examination she was deeply unconscious, with rigid limbs and extensor plantar responses. Her temperature was 101.4° F. (38.6° C.), pulse 110, and blood pressure 95/60 mm. Hg. Axillary hair was absent and pubic hair thin. The presence of a *Bact. coli* urinary infection was confirmed but she was not uraemic (blood urea 42 mg. per 100 ml., plasma sodium 144 and potassium 4.4 mEq per litre). Shortly after admission a lumbar puncture was performed, following which, and without therapy, she recovered consciousness. The cerebrospinal pressure was normal and the fluid clear, sterile, and acellular, and containing glucose 54 mg., chlorides 650 mg., and protein 70 mg. per 100 ml. She remained febrile—102–104° F. (38.9–40° C.)—despite antibiotic therapy, and two days after admission, following a convulsion, she again became unconscious, with spastic limbs and extensor plantar responses. The blood sugar was then 49 mg. per 100 ml. and the blood pressure 110/70. Continued infusion of 5% glucose caused only a transient return of consciousness, and she died in coma the following day. Several hours before death her blood pressure fell to 65/35. Other preterminal findings were: blood sugar 82 mg. per 100 ml.; plasma protein, 5.8 g. (albumin 3.2 g., globulin 2.6 g.) %; plasma sodium 153, potassium 3.9, and chloride 117 mEq per litre; blood culture negative; cerebrospinal fluid—low pressure, clear and colourless, red blood cells 47, white blood cells 30 per c.mm. (lymphocytes 70%), glucose 51 mg., chloride 740 mg., and protein 50 mg. per 100 ml.

At necropsy (Dr. I. Doniach) there were no abnormal findings in the central nervous system, heart, or lungs. The pituitary gland weighed only 350 mg. (normal 1 g.). There was extensive organized infarction of the anterior lobe, and at the periphery there remained only a few groups of eosinophil and chromophobe cells, which showed abnormal staining reactions. These changes extended into the pituitary stalk. The thyroid gland weighed 23 g. and showed flattened epithelium surrounding hyperchromatic inactive colloid. The adrenal glands showed marked cortical atrophy, involving especially the zona glomerulosa, and a low lipoid content. The ovaries were atrophic and showed minimal follicular development. The breasts were poorly developed and showed degenerative changes in the epithelium and periductal fibrous tissue and absence of secretion. The left kidney showed pyelonephritis with multiple small abscesses.

Coma in this case was precipitated by an acute renal infection. Although the patient was hypoglycaemic during the second period of coma, consciousness was restored for only a few hours by continued glucose infusions.

4. Hypoglycaemia

In hypopituitarism, hypoglycaemia may occur spontaneously, as in one of our patients (I. F., blood sugar 43 mg. per 100 ml.), during infections (Wilson, 1953), or following injection of insulin. Fraser and Smith (1941) stressed the value of the intravenous insulin-tolerance test in the diagnosis of panhypopituitarism. They also gave warning of its possible dangers and advised using only one-third of the standard dose of 0.1 unit insulin per kg. body weight when severe hypopituitarism is suspected. Rolland and Matthews (1952) reported severe hypoglycaemic symptoms in a man with hypopituitarism after 1.5 units of insulin, and Haussmann *et al.* (1951) induced hypoglycaemic shock with 1.75 units of insulin in a woman with Simmonds's disease who then remained semicomatose for two weeks despite energetic treatment.

Although not infrequently there is a normal response to this smaller dose in patients with undoubted hypopituitarism, severe reactions may still occur. One of our patients (I. K.) became comatose within 45 minutes of receiving one-third of the standard dose, and another (S. M.) became pale, sweated, and collapsed in coma with twitching of the limbs within 15 minutes of receiving half the standard dose of insulin. Consciousness returned with infusion of glucose.

Insulin may also be given for other than diagnostic reasons to patients not yet known to have hypopituitarism. Oliver (1952) described the case of a man with pituitary tuberculoma, who died after two injections of 10 units of soluble insulin, given to promote appetite. Oversensitivity to insulin therapy is also shown by the following very unusual case, in which diabetes mellitus was modified by the progression of hypopituitarism.

E. K. suffered a severe post-partum haemorrhage after the birth of her second child when she was 32. Lactation failed but menstruation returned three months later, to remain scanty and infrequent until it ceased at 39. At 44 she developed diabetes mellitus, which did not require more than 24 units of soluble insulin for its control. At 52, when recovering from severe influenza, she passed into deep coma five hours after an injection of soluble insulin (10 units), despite having taken her normal breakfast and lunch. It needed 100 ml. of 50% glucose, intravenously, to restore consciousness. On then withholding insulin for 48 hours, she became drowsy and ketotic (blood sugar 440 mg. per 100 ml.), and at this point soluble insulin (10 units) again caused hypoglycaemic coma. She had no pubic hair, and hypopituitarism with secondary adrenal failure was subsequently confirmed. After many more hypoglycaemic attacks, her diabetes was eventually controlled by a balanced use of cortisone and insulin. She has since gained 21 lb. (9.5 kg.) in weight and has remained well for over a year.

5. Hypersensitivity to Drugs and Anaesthesia

As in Addison's disease, so also in hypopituitarism, there is hypersensitivity to drugs and anaesthesia. In one of our patients an injection of morphine sulphate, ¼ gr. (16 mg.), before a minor operation induced coma which lasted for two days. In another, coma followed quinalbarbitone, 1½ gr. (0.1 g.), and pethidine, 50 mg. Another passed quickly into the third stage of anaesthesia after pentobarbitone sodium, 1½ gr. (0.1 g.), and less than 4 ml. of intravenous thiopentone sodium, recovering in the course of two days.

6. Sodium Depletion

It is still uncertain to what extent the pituitary gland controls the adrenal secretion of mineralocorticoids. Even in advanced hypopituitarism it is unusual to find a classical adrenal crisis in which coma accompanies severe sodium depletion, azotaemia, and circulatory collapse. Laws (1952) has described modified crises of this type in two patients with post-partum pituitary necrosis. Both had been treated for long periods with thyroid extract for supposed primary myxoedema. One died during a second crisis; the other recovered, to die later after influenza.

A sodium-losing crisis, with coma, occurred in two of our cases of pituitary necrosis. In the first (I. F., already described) this happened once in response to pneumonia and again during acute gastro-enteritis (Fig. 2). In the second patient (J. B.) severe sodium depletion was probably precipitated by cortisone therapy.* In this instance coma, acute loss of weight, and extreme circulatory collapse (blood pressure unrecordable) were preceded by psychotic symptoms and probably aggravated by a paraldehyde injection (10 ml.). A few hours before the onset of coma the plasma sodium had fallen to 117 mEq per litre. The coma was corrected within 12 hours by intravenous saline, cortisone, and D.C.A., although full recovery took several days.

Although sodium depletion sufficient to cause collapse seldom occurs spontaneously in these patients, loss of this ion during surgery, infections, or gastro-enteritis is not well tolerated, and may be a critical factor in precipitating coma.

*In Addison's disease and hypopituitarism the sodium excretion may rise greatly during the first few days of cortisone therapy. The same phenomenon occurs, and with greater regularity, in the adrenalectomized dog, and is due to a rise in the glomerular filtration rate (Garrod *et al.*, unpublished observations).

7. Water Retention

Patients with hypopituitarism cannot excrete a water load rapidly, a failure which is readily corrected by cortisone (Garrod and Burston, 1952). They are more prone, therefore, to water intoxication; and this can occur either after a water-loading test or spontaneously, and may be associated with changes in consciousness, as illustrated by the following patient, whose episode of sodium depletion has already been described.

J B., a housewife aged 53, suffered from severe hypopituitarism following a post-partum haemorrhage at the age of 40. During her first admission to hospital she became drowsy and confused the day after a water diuresis test. She had excreted only 9% of the water dose in four hours, and oliguria had continued. She complained of nausea and anorexia. The blood pressure was 100/70 mm. Hg and the blood urea 21 mg. per 100 ml. The plasma sodium was only 116 and chloride only 85 mEq per litre. She was given 200 mg. of cortisone and 5 mg. D.C.A. during two days, which caused a large water diuresis, loss of weight, and early recovery of her mental state.

When admitted to hospital one year later, having relapsed because she had failed to continue treatment, she gained 2.5 kg. in weight from fluid retention during 10 days without treatment and became drowsy, confused, and irritable, with loss of appetite. The blood pressure was 120/90 mm. Hg and there were no signs of heart failure. The plasma sodium had fallen from 130 mEq per litre on admission to the very low level of 107 mEq. She was given 200 mg. of cortisone by mouth and intravenously and 10 mg. of D.C.A. by intramuscular injection, followed by 75 mg. of oral cortisone daily. During the first two days of treatment she passed 3.1 litres of urine with a minimal sodium content and lost 2 kg. in weight. By the third day her plasma sodium had risen to 130 mEq per litre. Her mental state cleared within a day of starting treatment.

8. Cerebral Anoxia

Six of our patients were subject to hypotensive postural faints which seemed to be due to cerebral anoxia. One patient (S. M.) fainted when he stood up after a hypoglycaemic attack. Another (J. H.) became confused during a short flight at average height in a commercial air liner. Severe postural hypotension is more likely to occur when the hypothalamus is also involved, as seemed probable in the following patient with a craniopharyngioma.

I. K., a tailor's machinist aged 63, was first seen by one of us (O. G.) in 1948. Three years previously he had collapsed unconscious while at work, and had fainted the next day on standing up. His vision had steadily failed until latterly he had been unable to read or write. He had become increasingly inactive and had often lost consciousness for several minutes on rising from his bed. While in another hospital death had twice seemed imminent when he was found cold and pulseless after fainting attacks. On examination, despite his having had testosterone, he was pale and wasted, with dry inelastic skin and diminished facial and pubic hair. He lay apathetically in bed, yawning frequently, and resenting examination. Both eyes contained early cataracts; the right was almost totally blind, the left showed complete temporal hemianopia. His blood pressure, reclining, was usually around 150/80. After three minutes of sitting with his legs dependent it fell to 75/50. One minute later it could not be recorded and he became pale and unconscious. He recovered consciousness within five minutes of raising the foot of his bed, but after reclining for a further 40 minutes his blood pressure was still only 90/60. On further investigation he was found to have a large pituitary fossa, with destruction of the clinoid processes and slight suprasellar calcification, and hypopituitarism with secondary adrenal failure was confirmed (see Table).

9. Hypothermia

These patients are usually intolerant of the cold, and one (I. F.) said that she became mentally confused during cold weather. In one of the post-operative cases the body temperature fell to 96° F. (35.6° C.), but consciousness did not return when this was raised to 99° F. (37.2° C.) by warming for six hours. Cooling of the body is known to cause progressive somnolence and unconsciousness. However, in the example just cited it is unlikely that hypothermia was caused by exposure to cold; more probably there was a failure of the heat-regulating centres. Injury to the hypothalamus is not essential, since Sheehan and Summers (1952) have described hypothermia in comatose patients with pituitary necrosis. It is uncertain how often hypothermia is a primary factor in initiating the coma. It might, however, be expected to occur during the exposure of an already unconscious patient to cold, and thus be a further factor in prolonging coma. Sheehan and Summers (1952) were able to restore consciousness in two of their patients by immersing them in a hot bath.

Discussion

(a) The Aetiology of Hypopituitary Coma

Many authors have stressed the importance of hypoglycaemia as a cause of "hypopituitary coma." We have found, however, that hypoglycaemia is an unusual finding in the early stages, or, indeed, throughout the comatose attacks, and that when present it is often of too slight a degree to explain by itself the severity of the disturbance of consciousness. Likewise we have failed to find any biochemical disorders that are a constant or even usual feature of these attacks. It is important, therefore, to consider the mechanism of coma in general, understanding of which has been advanced by recent studies of neuronal metabolism.

Consciousness has been defined as an awareness of environment and of self (Cobb, 1948). Although consciousness was once believed to be integrated entirely within the cerebral cortex, it has now been shown to depend also on certain critical centres within the thalamus, hypothalamus, and reticular area of the mid-brain (Cairns, 1952). Any disturbance of neuronal metabolism within the centres of consciousness may affect the mental state. Energy released within nerve cells is derived almost entirely from oxidation of glucose and glutamic acid, a process which may be hindered by interference with specific enzyme systems, by lack of substrate, or by anoxia. In addition, mechanical effects such as trauma, pressure, or oedema may block the delivery of substrate or oxygen to critical areas of the brain (Fazekas and Bessman, 1953). In severe hypopituitarism the centres of consciousness are probably unduly vulnerable because of changes within the cerebral cells resulting from endocrine deficiencies, and from impairment of that part of the defence mechanism which is mediated through the pituitary–adrenal axis. If we can exclude certain post-operative cases in which local factors may be important, it would seem that disorders of consciousness are unlikely to arise in hypopituitarism unless the peripheral endocrine failure is well advanced.

Poor adrenal function is a more constant finding than thyroid failure in these cases; and our experience also points to the effectiveness of cortisone in protecting consciousness during periods of metabolic stress. Although adrenal function in these patients may be just adequate for their lowered metabolic needs, yet in the presence of infection, hypoglycaemia, or other stresses it is probably unable to respond further owing to lack of stimulation by the pituitary gland. We believe that this may be a fundamental factor in allowing the mental changes to occur, and that consciousness can usually be protected if exogenous cortisone be provided. In the post-operative cases of pituitary tumour further factors that may predispose to coma are trauma, local oedema, and a transient mechanical interruption of portal pathways between the hypothalamus and anterior pituitary gland.

(b) Diagnosis of Hypopituitary Coma

The possibility of hypopituitarism should always be considered when the cause of coma is obscure. In a woman the diagnosis would be supported by an earlier history of sepsis or post-partum haemorrhage, followed by a failure of lactation and amenorrhoea, or by scanty menses culminating in a premature menopause. Other symptoms that might be elicited from the husband or other relatives are loss of libido, asthenia, fainting attacks, hypersomnia, and undue sensi-

tivity to cold. In either sex a history of headaches or visual failure, or evidence of primary optic atrophy, should lead to an early *x*-ray examination of the pituitary fossa.

As hypopituitarism progresses gonadal function is the first to fail, followed usually by adrenal and, finally, by thyroid failure (Garrod and Gilliland, 1954). Adrenal and thyroid failure are not easy to recognize clinically in their early stages, and in order to demonstrate the changes certain tests are needed which we do not propose to discuss in this paper. When the disease is far enough advanced for coma to arise, and if testosterone or oestrogens have not already been given, there should always be some clinical evidence of hypogonadism. In a comatose patient, any of the following signs should arouse a suspicion of hypopituitarism: loss of pubic and axillary hair, atrophy of the labia minora and vaginal epithelium, a small uterus; and in the male, paucity of beard and body hair, a small prostate gland, and soft testes. Further suggestive findings are loss of pigment in the nipples and areolae in the female, and, in both sexes, pallor and a soft thin skin. In severe or long-standing cases the patient may present with a classical appearance of myxoedema, and when coma occurs in a myxoedematous patient a pituitary origin should always be suspected, and cortisone given if there is any doubt.

A combination of hypotension, azotaemia, and haemoconcentration suggests loss of sodium from adrenal failure, in which case the depletion may be masked by haemoconcentration, although urinary sodium excretion should be higher than in shock arising from other causes. In a confused or drowsy patient a very low plasma sodium, with normal blood urea and a normal or only slightly lowered blood pressure, suggest water intoxication.

(c) The Management of Hypopituitarism in Relation to Coma

Study of these cases points the way to a more effective management of hypopituitarism and of the mental changes associated with it. It is not our purpose here to discuss the therapy of hypopituitarism in general, but only in so far as it effects these disturbances of consciousness.

Prevention of Coma.—From our own experience, and from unpublished observations of others, it seems likely that with regular cortisone therapy these patients will be protected from hypersomnia and "hypopituitary coma," provided that the daily dose is increased during intercurrent infections, surgery, and other stresses. The advent of this hormone has undoubtedly improved the general outlook in these patients. Oral cortisone, 12.5 to 25 mg. a day, should be given indefinitely to all patients with hypopituitarism who show signs of diminished adrenocortical function such as hypotension, failure of water diuresis, increased insulin sensitivity, or depressed voltage or low T waves in the electrocardiogram. If in addition there is clinical evidence of hypothyroidism or laboratory evidence such as raised plasma cholesterol or a basal metabolic rate of less than −25%, or if the electrocardiographic abnormalities cannot be corrected by cortisone alone (Garrod and Gilliland, 1954), a daily dose of L-thyroxine 0.1–0.2 mg., or thyroid extract, 1 to 2 gr. (0.06–0.13 g.), should also be given. Testosterone therapy, whilst usually needed to improve sexual function and promote protein anabolism, seems to afford incomplete protection against the risks of coma.

Infections.—We have discussed the hazard of infections such as influenza and gastro-enteritis. Although patients cannot hope to escape these entirely, they can avoid crowds and known infection in other persons. Acute infections, even colds, should be treated promptly, under ideal conditions of rest in bed, and the dose of cortisone increased, temporarily, to at least 50 mg. a day.

Anaesthesia and Surgery.—Whenever possible general anaesthesia should be avoided and surgery restricted to emergencies. When operation becomes inevitable it should be carried out under full cortisone cover of at least 100 mg. a day. Likewise, cortisone should be used in operations on the pituitary gland, whether or not there is prior evidence of hypopituitarism, since it is possible that post-operative trauma in this region may block hypothalamic-pituitary pathways through which adrenal response to stress is mediated. The effectiveness of cortisone in the surgery of suprasellar tumours has already been shown by Ingraham *et al.* (1952) and by recent experience in the Department of Neurosurgery at Dunedin (Mr. Anthony James).

Insulin.—In view of the great susceptibility of these patients to insulin and the difficulty there may be in correcting hypoglycaemic coma, even when the blood sugar has been restored, we feel that the insulin-tolerance test is probably an unjustifiable risk when the diagnosis of hypopituitarism can be made by other means. Its main application would seem to be in doubtful cases with little evidence of adrenocortical failure. Unfortunately, a negative response to the smaller test dose does not exclude hypopituitarism.

Drugs.—Hypnotics and analgesics must be used sparingly, and morphine and allied compounds should not be given.

The Treatment of "Hypopituitary" Coma

Opinions have varied regarding the optimal management of this condition, and the assessment of therapeutic measures is made difficult because of a tendency to spontaneous recovery once the precipitating factors have ceased to act. Also it is possible that irreversible changes within the brain may have occurred by the time therapy is instituted (Wilson, 1943). Allott and Simmons (1951) described a patient whose coma failed to respond to D.C.A. and infusion of glucose–saline, but who regained consciousness within 24 hours of receiving cortisone, and Decourt *et al.* (1954) have described a similar response. Caughey *et al.* (1952) reported three cases of coma: in one there was a good response six days after starting treatment with testosterone and thyroid extract, 1½ gr. (0.1 g.) a day; the second responded to cortisone alone, and the third to combined cortisone and A.C.T.H. If cortisone had been given orally, rather than by intramuscular injection, the response would probably have been more rapid.

As a result of further experience we now recommend the following therapeutic plan. As soon as coma is found to be associated with hypopituitarism, and especially when there is fever, search should be made for signs of a precipitating infection such as influenza, pneumonia, pyelitis, or gastro-enteritis, and appropriate antibiotic therapy started at once. If the body temperature is very low the patient should be immersed in a warm bath (Sheehan and Summers, 1952). In all cases the rectal temperature, pulse rate, and blood pressure should be checked at short intervals. Blood should be taken early for estimation of blood sugar, plasma sodium, urea, bicarbonate, and haematocrit or plasma specific gravity. Without waiting for the results, and on the supposition that hypoglycaemia may be present, glucose should then be given by mouth if the patient can be roused, or by intravenous injection (50 ml. of 50% glucose followed by a steady infusion of 5% glucose). To get the quickest glucocorticoid effect, hydrocortisone (compound F) is preferable to cortisone; and, because absorption from the gut may be delayed, intravenous therapy is more effective than oral. An infusion of 50 to 100 mg. of hydrocortisone alcohol dissolved in 250 to 500 ml. of isotonic saline should be given as soon as possible. If hydrocortisone is not available, 50 to 100 mg. of microcrystalline cortisone acetate ("cortone") can be given intravenously. Thereafter, 50 mg. of cortisone acetate should be given six-hourly by nasal tube, which should be kept *in situ* for feeding purposes, until consciousness has been regained.

Further treatment must be regulated by the clinical and biochemical findings. If hypoglycaemia is present, intravenous or oral glucose should be continued. The presence of hypotension, haemoconcentration, azotaemia, and sodium depletion (the latter may be masked by haemoconcentration) calls for intramuscular injection of 10 mg. of D.C.A. and an adequate sodium intake. In any event it may be wise to give 5 mg. of D.C.A. during the first few days because cortisone may initially increase the sodium output, probably by raising the low glomerular filtration rate, and is too weak a

sodium-retainer to correct quickly any serious depletion of this ion.* If there is excessive water retention cortisone will correct this by allowing the selective excretion of water in excess of sodium (Garrod and Wynn, 1954).

Since coma occurs in patients with hypopituitarism who are already receiving thyroid extract and testosterone, it is doubtful whether these hormones are of much value in the acute management of this condition. However, if there is obvious myxoedema, L-thyroxine or thyroid extract should be given as well as cortisone and D.C.A., with full awareness that their metabolic effects will be delayed.

Summary

Disturbances of consciousness which varied from hypersomnia, mild confusion, and impaired cerebration to stupor and profound coma were encountered in 17 patients with hypopituitarism.

There were many factors which precipitated coma, and these included cerebral surgery, pituitary apoplexy, infections, hypoglycaemia, drugs and anaesthetics, electrolyte disturbances, water intoxication, and cerebral anoxia.

Except in some of the post-operative cases, severe endocrine failure, especially of the adrenal cortex, seemed to be an essential factor in lowering the threshold of consciousness. Cortisone was more effective than thyroxine or testosterone in the prevention and correction of coma.

In obscure cases of coma the possibility of hypopituitarism should always be considered. The diagnosis, prevention, and treatment of "hypopituitary coma" are discussed in the light of further experience.

We are grateful to many physicians in New Zealand and the United Kingdom who have given us access to their cases; to Mr. Anthony James, neurosurgeon of the Dunedin Hospital; and to Dr. C. L. Cope and Dr. T. Russell Fraser, under whose care some of these patients were studied. We are grateful for secretarial assistance from Miss D. E. Hunt and Miss G. M. Turner.

ADDENDUM.—Since this paper was submitted for publication Whittaker and Whitehead (1954) have described a case of hypopituitary coma arising from water intoxication, and a case of coma due to hypothermia in a patient with hypopituitarism who was already receiving cortisone therapy.

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*See footnote on p. 557.

EFFECT OF CHLORPROMAZINE ON THE BEHAVIOUR OF CHRONICALLY OVERACTIVE PSYCHOTIC PATIENTS

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Reports of the varied central effects of chlorpromazine hydrochloride ("largactil") (Laborit and Huguenard, 1951; Courvoisier *et al.*, 1953; Brand *et al.*, 1954), its reputed potentiating action on central depressants (Laborit and Jaulmes, 1952; Courvoisier *et al.*, 1953), and the clinical response observed in various psychiatric states (Delay, Deniker, and Harl, 1952a, 1952b; Delay, Deniker, Harl, and Grasset, 1952; Delay and Deniker, 1953; Sigwald and Bouttier, 1953) have encouraged a limited trial of this drug in regard to its effect on the behaviour of a small group of chronically overactive psychotic patients in a large and overcrowded mental hospital.

Clinical Material

The material (Tables I and II) consisted of 12 male patients and 15 female patients drawn from the disturbed ("refractory") wards of the hospital. These patients were chosen less according to diagnostic category than because of the degree of overactivity they exhibited, which was sufficient to make them a persistent and difficult nursing problem. Of the 27 patients, 10 were diagnosed as schizophrenics and 3 as paraphrenics. These are grouped together in our assessment as suffering from schizophrenic disorders. Seven cases (Nos. 2, 5, 8, 9, 10, 11, and 14) suffered from recurrent or chronic hypomania, one (Case 13) was a manic-depressive, and three cases (Nos. 4, 7, and 24) were chronic agitated melancholics; these formed the affective group. The remaining three (Cases 20, 21, and 22) were confused, restless, overactive female senile dements. Three cases (Nos. 5, 13, and 14) in the affective group and one paraphrenic (Case 15) showed signs of organic cerebral deterioration, and one chronic melancholic (Case 24) had had a leucotomy performed six years ago, after which she had become more destructive and even incontinent.

The medical and nursing staff were thoroughly familiar with the pattern of each patient's illness, and this was taken into account when assessing results.

Design of Trial

The patients were mostly observed in their own wards, but where they were transferred from one ward to another an equilibration period of two weeks was allowed. During this time patients were given an opportunity to adjust to their new environment, and full account was taken of any day-to-day variation shown. Within seven days of the beginning of the trial all sedatives were withdrawn. Chlorpromazine tablets and inert control tablets were then administered to the same patient in alternating periods for the duration of the trial. Only one observer (C. E.) and the dispenser knew which patients were receiving the active or

TABLE I.—*Summary of Clinical Material, Total Dosage, and Response*

No.	Age and Sex	Age on First Admission	No. of Admissions	Present Hospitalization (Years)	Diagnosis	Previous Physical Treatment	Total No. of Chlorpromazine Tablets Received During Trial and Total Dosage	Total No. Placebo Tablets Received During Trial	No. of Times Placebo and Chlorpromazine were Alternated	Therapeutic Response	Body Weight Difference at End of Trial	
											lb.	kg.
1	62 F	60	1	2	Paraphrenia	—	574 (14,350 mg.)	488	7	Definitely improved	−5	2·3
2†	54 F	53	1	1	Manic-depressive psychosis; recurrent hypomania	E.C.T.	410 (10,250 mg.)	252	3	„	+30½	13·8
3	32 M	18	2	6	Schizophrenia	E.C.T.	504 (12,600 mg.)	504	3	„	+11	5·0
4	52 F	41	At least 3	5	Chronic agitated melancholia	E.C.T.	768 (19,200 mg.)	294	3	„	+34	15·4
5*	69 M	18	4	15	Manic-depressive psychosis; recurrent mania	—	546 (13,650 mg.)	378	3	„	+6	2·7
6	46 M	22	3	9	Schizophrenia	E.C.T.	434 (10,850 mg.)	430	4	„	+17	7·7
7	54 F	36	1	18	Chronic agitated melancholia	—	553 (13,825 mg.)	224	7	„	+23	10·4
8	49 F	42	2	2½	Manic-depressive psychosis; recurrent hypomania	E.C.T.	448 (11,200 mg.)	504	6	Slightly improved	+6	2·7
9	43 F	41	1	2½	Mixed (schizo-affective) psychosis	E.C.T.	469 (11,725 mg.)	294	5	„	+14	6·4
10†	49 F	34	3	1½	Manic-depressive psychosis; recurrent mania	E.C.T.	483 (12,075 mg.)	208	2	„	+17½	7·9
11‡	40 F	38	1	1½	„ „ „	E.C.T.	402 (10,050 mg.)	210	2	„	+14	6·4
12	48 F	43	1	4	Paraphrenia	E.C.T.	419 (10,475 mg.)	404	5	„	+2	0·9
13*	45 M	38	2	7	Manic-depressive psychosis	—	420 (10,500 mg.)	462	3	„	+3	1·4
14*	67 M	50	6	11	Manic-depressive psychosis; chronic hypomanic state	—	298 (7,450 mg.)	282	4	„	+1	0·45
15*	73 M	58	1	15	Paraphrenia	—	354 (8,850 mg.)	336	4	„	+3	1·4
16	43 M	21	1	22	Schizophrenia	Contin: narcosis and maintenance E.C.T.	455 (11,375 mg.)	416	4	„	+2½	1·1
17	42 M	28	3	14	„	—	518 (12,950 mg.)	478	5	„	−6	6·4
18	46 M	?16	2	11	„	E.C.T.	547 (13,675 mg.)	406	4	„	+11	5·0
19	39 M	21	1	19	„	E.C.T.	345 (8,625 mg.)	420	3	Not improved	+13	5·9
20	75 F	73	1	2	Senile dementia	—	510 (12,750 mg.)	384	3	„	+3	1·4
21§	85 F	84	1	1	„ „	—	175 (4,375 mg.)	102	3	„	+5	2·3
22	71 F	70	1	1	„ „	—	434 (10,850 mg.)	416	5	„	+6	2·7
23	44 F	34	1	10	Schizophrenia	Contin: narcosis E.C.T.	493 (12,325 mg.)	376	3	„	+1	0·45
24§	59 F	45	1	14	Chronic agitated melancholia (post-leucotomy)	E.C.T. Leucotomy	231 (5,775 mg.)	147	3	„	+6	2·7
25	29 F	26	4	2½	Schizophrenia	Insulin-coma E.C.T.	378 (9,450 mg.)	322	5	„	+2	0·9
26	32 M	23	?	5½	„	Insulin-coma E.C.T.	385 (9,625 mg.)	332	3	„	+5	2·3
27	50 M	28	1	22	„	E.C.T.	448 (11,200 mg.)	420	5	„	+2	0·9

* These patients showed signs of organic cerebral deterioration. † These patients were included in the trial six weeks later than the others.
‡ This patient was included in the trial seven weeks later than the others. § These patients were withdrawn from the trial after eight weeks.

the inactive preparation at any given time; the medical staff and the day and night nursing staff taking part in the assessment of results were not in possession of this information.

Dosage

To begin with, the effective dose of the drug and the length of the period of continuous medication were a matter of trial and error. Weekly alternation between the active and inert control tablets was tried first; this was followed by the administration of active and placebo tablets in blocks of three weeks at a time. As the trial progressed, however, it was found that clinical changes, in terms of both improvement and relapse, were slow to develop, and a six-weeks period appeared more adequate for judging the effects of the preparation. Consequently, from the seventh and eighth weeks onwards most of the patients received the drug in six-week blocks. The total dosage of drug and placebo are given in Table I. Although administration usually began with 75 mg. by mouth—one 25-mg. tablet t.d.s.—up to 300 mg. a day was given transitorily in most cases. These high dosages led to undesirable side-effects, and ultimately 150 mg. (two tablets t.d.s.) was found to be both safe and (in those cases in which response was noted) effective. A smaller maintenance dose has not been tried in the present series. The only exception to this was Case 4, in which signs of relapse were noted when the dose was reduced from 150 mg. to 100 mg. a day. The trial lasted for 22 weeks.

In only three cases (Nos. 2, 10, and 11) was the drug given by the intramuscular route. These cases were included in the trial somewhat later than the others, and at the time were suffering from acute hypomanic states. Each received three injections (of 25 mg.) daily for one week, and a total of 100 mg. daily during the second and third weeks. No pain was complained of, but as there was some induration at the site of the injection this route was abandoned and medication by mouth (at 150 mg. a day) substituted.

TABLE II.—*Clinical Material*

	Affective Disorders	Schizophrenic Disorders	Senile Disorders	Total
Male	3	9	0	12
Female	8	4	3	15
Total ..	11	13	3	27

Clinical Assessment and Recording of Results

Each patient was seen daily by the observer in charge of the trial (C. E.), and at weekly intervals by two medical

officers. The day and night nursing staff also took part in the trial, the aim being to cover the relevant aspects of the patient's behaviour "round the clock." The day nursing staff were asked to write a daily note on each patient. This covered their general behaviour in the ward, their social attitudes, eating habit, work, and particularly their periods of overactivity and impulsiveness. The night nurses noted restlessness, noisiness, and sleep. The medical observers' findings were recorded in two ways. The first was the usual clinical note, which was made at a weekly interview and did not take into account the day-to-day behaviour in the ward. In addition, however, an attempt was made to itemize (though not score) the various relevant aspects of the patient's mental state and behaviour. "Pro-forma" sheets covering these items were designed in consecutive discussions with the medical staff and used as the patients were seen week by week. These "pro-formas" are still undergoing trial, and will be the subject of a separate communication when complete. Nevertheless, even in their present form they ensured that certain aspects of the clinical picture were always looked for, and no information was lost by default. Assessment was made by one of us (C. E.) at the end of each week on the basis of daily personal observation and of these daily (nurses') and weekly (medical observers') reports; and a final assessment was made again at the end of the trial—that is, after 22 weeks. It is well to remark here that it was the nurses' daily written reports which were found to be particularly useful when analysing results in retrospect. They often served to emphasize changes which might otherwise have been overlooked.

The combination of the "blind" nature of the trial, the fact that the patient was used as his own control, and agreement among the different observers, all contributed towards some confidence in a field in which assessment is notoriously difficult. Our findings so far suggest that chlorpromazine may have its place in the symptomatic treatment of a limited proportion of chronically agitated psychotic patients.

Results

During the first two weeks of the trial nearly all the patients seemed better, irrespective of whether they were receiving the active or inert preparation. They became quieter and more responsive, and one patient (Case 24) ceased to be incontinent and destructive of clothing. This effect, however, was transient, and relapse to the behaviour usual for each patient was not long in forthcoming, except in those in whom a genuine response to the drug was observed. It seems likely that this illusory improvement was due to the unaccustomed daily attention which the patients were getting, and their knowledge that they were undergoing a new kind of treatment. The staff's enthusiasm, too, soon found its own level, and as the weeks went by the effects of chlorpromazine could be more clearly distinguished.

In the responses grouped in Table III the term "definitely improved" is applied to those cases in which the improvement was undoubtedly attributable to the drug. This was judged by the improvement as medication proceeded, the relapse when placebo therapy was substituted, and the reappearance of improvement when the active preparation was reinstated. The patients became quieter, less tense, and less disturbed by their hallucinations and delusions during the weeks they were receiving chlorpromazine; their eating, sleep, and social habits changed for the better, and two (Cases 3 and 6) could be allowed privileges or enjoy occupations which they could not have followed before. In three cases (Nos. 3, 4, and 5) parole was considered—in one of them (Case 5) for the first time in fifteen years. As the inert control tablets were substituted, the behaviour of the patients gradually became more disturbed, although, with the exception of two cases (Nos. 1 and 7), overactivity never quite reached its former level. In one instance, however (Case 4), the patient, after two weeks on placebo tablets, became so unmanageable that chlorpromazine had to be resumed. This patient improved within one week. The cases subject to recurrent attacks of mania (Cases 2 and 5) were given chlorpromazine at a time coinciding with the onset of their overactive phase; this reduced their overactivity to below the level usual for these patients.

TABLE III

	Definitely Improved		Slightly Improved		Not Improved	
	Male	Female	Male	Female	Male	Female
Affective disorders	1	3	2	4	0	1
Schizophrenic disorders	2	1	4	1	3	2
Senile	0	0	0	0	0	3
Total ..	7		11		9	

The cases designated "slightly improved" did not show the same clear-cut response. In one group (Cases 9, 12, 15, 16, 17, and 18) there was a gradual lessening of overactivity during chlorpromazine medication, although noisy outbursts in response to hallucinations continued. It was only after prolonged periods (four to six weeks) on placebo that it was noticed that the periods of overactivity during active medication had been less frequent and far less intense than during the placebo period. The other group included five patients (Cases 8, 10, 11, 13, and 14) subject to cyclic disorders. The phasic nature of their overactivity remained basically unaltered; but the extent of their overactivity was somewhat reduced.

The term "not improved" was applied to those cases in which no improvement of any kind could be attributed to chlorpromazine. Included in this group are five schizophrenics (Cases 19, 23, 25, 26, and 27) and the only three cases of senile dementia (Cases 20, 21, and 22) in the trial. There was also one patient (Case 24) with agitated melancholia who had had prefrontal leucotomy performed six years ago, and another (Case 21) in whom the trial was cut short after eight weeks owing to the patient's poor physical state: although, in retrospect, and in the light of further experience with the drug, continued medication would have seemed permissible.

It is important to stress that in no case was the content of the psychosis changed. The schizophrenic and paraphrenic patients continued to be subject to delusions and hallucinations, though they appeared to be less disturbed by them. Those patients who suffered from recurrent attacks of hypomania became less excitable and aggressive during these phases, though their affective swings continued at intervals normal to each patient. The chronically agitated melancholics, while becoming less tense and at times apparently less miserable, did not themselves admit to any improvement in their mental state. Few of these chronic psychotic patients showed improvement which enabled them to become more useful members of the mental hospital society. Others became less difficult nursing problems. Three were considered fit for parole, but none were thought fit for discharge. The relief afforded by chlorpromazine thus appears to be principally symptomatic.

The following notes illustrate the type of change observed.

Improved Cases

Case 3.—A 32-year-old schizophrenic man had been in this hospital for six years. He was on escape caution, and was unemployable. His behaviour was greatly disturbed by terrifying visual and auditory hallucinations. He referred to them as "bogies," and, when present, they occupied his whole attention. He spent a great deal of time writing inconsequential sentences, or drawing to "ward off the bogies," and he would often shout abuse at them, banging the furniture, and marching about the ward. His sleep was disturbed, and he required sedation nearly every night. Socially he was very withdrawn and solitary. After three weeks on chlorpromazine he gradually became more accessible and friendly. He worked on the ward, took charge of Christmas decorations, and escape caution was discontinued. Finally, he was able to attend occupational therapy

for the first time since his admission. Here he practised his talent for painting. He received no medication apart from chlorpromazine, and had only occasional restless nights despite this. Sporadically he would shout at his hallucinations, but he said that the "bogies did not worry him so much." He relapsed when on placebo tablets, and was graded as definitely improved. By the end of the trial he had gained 11 lb. (5 kg.) in weight.

Case 5.—A 69-year-old man who was subject to recurrent attacks of mania first became ill at the age of 18 years. He had been admitted four times, and had spent a total of 23 years of his life in this mental hospital. He now showed signs of organic cerebral deterioration. His behaviour was usually quiet, though somewhat elated, but he had regular periods of extreme overactivity when he would constantly run round the ward singing and shouting until he was hoarse. At these times he was quite incapable of maintaining any contact or of any connected conversation. After chlorpromazine medication it was noted that, although his affective swings were not altered, his manic phases were less acute. He was less overactive and less constantly noisy; and, although still garrulous and showing flight of ideas, his attention could be held for very brief periods. During his quiet periods his affect seemed normal. His wife, who knew nothing of the trial, spontaneously remarked on how well he was. He was thought fit for parole for the first time in 15 years. He was graded definitely improved. Weight gain here was negligible.

Case 6.—A 46-year-old schizophrenic man fell ill when he was 22 years old. He had been admitted three times, and the length of the present admission was nine years. In the wards he was aimlessly overactive, often aggressive to other patients and staff, and frequently involved in fights and quarrels. At one time he had worked on the hospital farm, but had to be removed because of his impulsive behaviour. In conversation he appeared fairly well orientated but disconnected, and chattered away irrelevantly, using bizarre pseudo-psychiatric neologisms. He was domineering and often interfered with other patients, and his manner suggested hallucinations. After chlorpromazine medication, improvement was noticed only slowly. Although he continued to be rather domineering, he became much less aggressive, and was involved in no violent incidents after the first three weeks of the trial. He started working again on the farm, and did very well. His manner of speaking, however, was unchanged. Although he did not fully relapse on placebo tablets, he was graded as definitely improved because of the social change in him. He gained 17 lb. (7.7 kg.) in weight.

Case 4.—A 52-year-old chronic agitated melancholic woman, first admitted at the age of 41, was extremely tense and was tortured by delusions of guilt and persecution. Her mental state had not fluctuated for four years, except for temporary improvement after E.C.T. She had to be spoon-fed, refused to occupy herself, and spent a great deal of time weeping, and had once swallowed her wedding-ring in a suicidal attempt. After one week on chlorpromazine she became less tense, and, although often still depressed, there were frequent days when she was cheerful and sociable, helped with the ward work, and knitted for her grandchildren. Her relatives remarked on the change in her, although (as in Case 5) they knew nothing of the treatment she was having. She ate her meals spontaneously and with no difficulty, and gained 34 lb. (15.4 kg.) in weight. She relapsed quickly when on placebo medication and showed signs of relapse when the dose of chlorpromazine was reduced from 150 to 100 mg. during one week. She was graded definitely improved.

Case 7.—A 54-year-old chronic agitated melancholic woman, who had been in hospital for eighteen years, was extremely tense and miserable, and continually wandered round the ward wringing her hands in anguish. She was irritable, occasionally impulsive, and negativistic, and often had to be spoon-fed. She was often incontinent of urine. Within two weeks of chlorpromazine medication she became, at times, more talkative and cheerful and appeared less agitated. Although she continued to grumble eternally about the food, and continued to be incontinent, her appetite increased greatly, she required no spoon-feeding, and she gained 23 lb. (10.4 kg.) in weight. She relapsed on placebo tablets, and was graded definitely improved.

Case 2.—A 54-year-old woman, who was subject to recurrent attacks of hypomania, had been observed in hospital for one year. Just before treatment was begun she had been allowed home on a month's trial, but was returned to hospital in a state of acute overactivity. She was noisy, impulsive, and aggressive, and had to be nursed in a side room. Chlorpromazine was administered intramuscularly at first; during the second week on the drug she became more subdued in her overt behaviour, although her mood remained elated. At the first sign of her next overactive phase, chlorpromazine (by mouth) was reinstated. The patient continued to be elated and garrulous and to show flight of ideas; nevertheless, her behaviour was changed, and she was able to continue ward work for the whole of this time, a state quite unusual for her. She gained 30½ lb. (13.8 kg.) in weight, and was graded definitely improved.

Case 1.—A 62-year-old paraphrenic woman was greatly disturbed in her behaviour by auditory hallucinations. She used to scream abuse in response to these, particularly to a "Mr. Knock," who put "filthy thoughts into her mind." She was deluded against some members of the staff, whom she habitually screamed at and threatened, and often was impulsive and aggressive when annoyed by other patients. She spent most of her time scrubbing the floor in an obsessional manner, and talking and shouting almost continuously. After three weeks of chlorpromazine medication her overactivity continued, but she was much quieter in response to her hallucinations, and said "she did not bother any more with Mr. Knock," as he "did not annoy her so much." She became quite polite and friendly towards her *bêtes noires* among the staff, but was still occasionally stimulated by other patients. She relapsed on placebo tablets, and was graded definitely improved. She lost a negligible amount of weight.

Cases Slightly Improved

Of the slightly improved group, the following may serve as examples.

Case 16.—A 43-year-old schizophrenic man, admitted to this hospital 22 years ago, was extremely withdrawn, and barely answered questions in monosyllables. He was never still, but continuously paced or ran up and down the ward, clapping his hands together, and frequently reaching a pitch of such wildly screaming excitement that E.C.T. was needed to calm him. After the beginning of chlorpromazine medication his endless pacing and mannerisms were unaltered, and he was often noisy, but at no time did he reach a degree of excitement at which E.C.T. would have been considered necessary. He did not relapse during the placebo period, and was graded slightly improved. The gain in weight was negligible.

Case 12.—A 48-year-old paraphrenic woman, admitted four years ago, was subject to wildly excited outbursts of aggression against patients and staff in response to hallucinations. After three weeks of chlorpromazine medication she still continued to talk to her hallucinations, and was sometimes noisy in doing so; there were, however, no acute uncontrollable outbursts of aggression. There were signs of more disturbed behaviour during the sixth week after chlorpromazine had been withdrawn. She was graded slightly improved. Weight increase was negligible.

Case 8.—A 49-year-old woman, readmitted 2½ years ago, was subject to recurrent attacks of hypomania. During these periods she was continuously overactive, mischievous, and aggressive. When on chlorpromazine she seemed less aggressive during her overactive phases, and less scattered; on some days she was able to carry out ward work. When on placebo she did not relapse to the intensity of her usual manic attacks. She was consequently graded slightly improved. Weight increase was negligible.

Side-effects

With high doses of chlorpromazine (up to 300 mg. daily) slight depression and lethargy were noted in some patients (Cases 1, 3, 5, 8, 9, 12, 14, 17, 18, and 27). The patients did not appear well, moved slowly, and their faces bore a greyish drawn look. There was no cyanosis of the extremities, and no marked or consistent change in blood pressure could be detected. Subjectively, the patients complained only of slight and vague malaise. Somewhat similar symptoms were observed in Cases 3, 14, 17, and 27 during the second and third weeks of medication on moderate doses (150 mg. a day). These symptoms, however, lasted for only a few days, and no reduction of the dose was thought necessary. Although our patients were not instructed to lie down after taking their tablets, no symptoms attributable to postural hypotension were noted.

One patient (Case 13) developed transient jaundice during the sixth week of the trial. He had received progressively increasing doses of chlorpromazine (75 mg. rising to 300 mg. a day) for four weeks, and this was followed by two weeks' placebo medication. It was during this second week on placebo that jaundice was noted. Laboratory findings at the height of jaundice were: serum bilirubin, 6 mg. per 100 ml. (van den Bergh—direct reaction); thymol turbidity test, 1 unit; zinc sulphate test, 1 unit; cephalin cholesterol (24 hours) negative, (48 hours) negative; total serum proteins, 6.4 g.% (albumin 4.4 g., globulin 2 g.). The trial was temporarily suspended for six weeks; the jaundice cleared within ten days, and liver-function tests returned to normal within three weeks. At the end of six weeks it was thought safe to resume chlorpromazine medication at the level of 150 mg. a day. There was no recurrence of symptoms. No jaundice was seen in any other patient, and liver-function tests, which were performed fortnightly in all patients, showed no abnormality. The cause of this single incidence of jaundice must remain obscure.

Full blood counts were performed in all patients at fortnightly intervals during the trial. In only two cases was abnormality noted. Case 11 showed some polychromatic cells and basophilic stippling in the ninth week of the trial—that is, after seven weeks on chlorpromazine and two weeks on placebo control. The red count was 3,840,000; haemoglobin, 78% (11.5 g.); total white count 8,400. This change was transient and was not noted in subsequent blood counts. Another patient (Case 8) showed slight transient neutropenia during the thirteenth week of the trial, after three weeks of chlorpromazine and six weeks of placebo. The blood count, however, returned to normal and chlorpromazine medication was continued.

Changes in Weight

Nine patients put on weight steadily during the trial, the increase ranging from 11 to 34 lb. (5 to 15.4 kg.), gained in 22 weeks. All these patients belonged either to the definitely or to the slightly improved groups (Table I). They included two cases of chronic agitated melancholia (Cases 4 and 7), three cases of chronic or recurrent hypomania (Cases 2, 10, and 11), one case of chronic hypomania with schizoid features (Case 9), and three cases of schizophrenia (Cases 3, 6, and 18). The remaining eight patients showed fluctuation in their monthly weights within a range of −5 lb. to +6 lb. (−2.3 to +2.7 kg.). This was not regarded as significant. One patient (Case 19) had gained 13 lb. (5.9 kg.) by the end of the trial; but this increase had to be discounted, as his record showed a regular fluctuation by this amount for the last five years.

Comment

The limited aim of the above small trial was to determine the usefulness of chlorpromazine in the management of the overactive chronic psychotic patient in the overcrowded disturbed wards of a mental hospital. As mentioned above, the 27 patients comprising the clinical material were chosen, not according to diagnostic category, but solely on the strength of the overactivity which they exhibited. Nor were they segregated in a "chlorpromazine ward." It seemed to us important, at first, to establish the effect of the drug on the individual patient in his normal ward environment, where he mixed with and was exposed to the often provocative behaviour of untreated overactive patients. Also, rather than use matched groups, we have used the patient as his own control, and alternated the active with the inactive preparation. There is a good deal to be said for either method of conducting a clinical trial; nevertheless, the somewhat smaller group made possible by the self-controlled design permitted the frequent, continuous, and independent observation of the material upon which the assessment hinged.

In our experience the effects of chlorpromazine usually did not become fully apparent until after three to six weeks of continuous medication (at or around the level of 150 mg. a day). The results were not dramatic, but were often subtle and not fully appreciated until after the effect of the drug had worn off (either following substitution by placebo or discontinuation at the end of the trial). They do, however, warrant further study. Statistical analyses of our small numbers in terms of diagnostic category, mean age, and length of hospitalization are hazardous; nevertheless, we can but remark that, with the exception of one patient who had undergone leucotomy (Case 24), all cases in the affective group responded either definitely or slightly in terms of our criteria, whereas the unimproved group included five schizophrenics out of a total of thirteen, and the only three cases of senile dementia in the trial. A relatively young schizophrenic, however (Case 3), showed definite improvement, although two others of about the same age (Cases 25 and 26) did not.

The essentially symptomatic nature of the response has already been stressed, and cannot be overemphasized. Although affect became more subdued, and attitude and behaviour reflected this improvement, the ingrained psychotic thought disorder seemed to be unchanged. The patients in the definitely and slightly improved groups became quieter and more amenable to suggestion and guidance by the nursing staff, and could carry out simple ward tasks with some degree of enjoyment. None required extra sedation when on chlorpromazine. In two cases relatives spontaneously remarked upon the patients' improvement. Three were considered fit for parole, though none were thought fit for discharge. The reply to the question whether the drug may be useful in the management of the chronically overactive psychotic would thus appear to be a qualified "yes."

A further point of interest was the increase in weight of nine patients. All belonged to the definitely or slightly improved group. For the present we are inclined to attribute this to improved eating habit as the patients became less tense, less preoccupied, or less assaultive; though more direct metabolic effects of the drug cannot be excluded.

In terms of reduction of overactivity, our results are broadly in keeping with those reported from the Continent (Delay, Deniker, and Harl, 1952a, 1952b; Delay, Deniker, Harl, and Grasset, 1952; Delay and Deniker, 1953), though the more chronic nature of our material makes detailed comparison somewhat difficult. The transient and partial response in chronic schizophrenics has been commented on (Lehmann and Hanrahan, 1954). The response in Case 48, reported in another paper (Sigwald and Bouttier, 1953), in which "there was no disappearance of hallucinations, but the interpretation became less acute and there was no longer any complaint of menace or revenge," certainly calls to mind our own experience in Cases 1 and 3.* The calming effect in manic-depressive disorders has also been observed by others (Staehelin and Kielholz, 1953; Lehmann and Hanrahan, 1954). More recently, in this country, the effect of chlorpromazine in chronic schizophrenics has been examined by J. Carse and D. W. Kay (personal communication), with whom we have exchanged information throughout the

*Since submitting this paper for publication we have seen the paper by D. Anton-Stephens (*J. ment. Sci.*, 1954, **100**, 543). The "psychic indifference" cited by this author is in keeping with our own observations.

conduct of our own trial. In a controlled "blind" trial they used 62 patients, one group of which (32 patients) received chlorpromazine and another (30 patients) a placebo over five weeks. These authors conclude that there was improvement, significant at the 5% level, in the chlorpromazine-treated group, as compared with the group receiving control tablets, and that "there was a case for further investigation." In view of the chronic nature of both their material and ours, it should certainly be of interest to examine the effect of full doses of the drug (used both alone and in deliberate one-by-one combination with other drugs) in cases of recent psychotic illness. A systematic trial in neurotic tension states is also called for, and the effect on eating habit would suggest trial in anorexia nervosa.

Perhaps we may be allowed to draw attention to one last point—namely, the lessons we feel we have learnt from the trial itself. The research instrument in a trial of this sort being a group of people, and its conduct being inseparable from the individual use of words, we were impressed by the necessity for a "blind" and self-controlled design, and independent multiple documentation. Furthermore, we were equally impressed by the false picture apt to be conveyed if undue reliance was placed on interview alone, as conducted in the clinic room. The patients' behaviour in the ward was apt to be very different. For that reason the day and night nursing staff became indispensable and valued members of the observers' team. We were warmed and encouraged by the energy and care with which they did what was requested of them, provided this was clearly and simply set out at the beginning. A chronic "back" ward thus became a rather interesting place to work in. There may well be a case for training senior nursing staff in elementary research method and in medical documentation. This would make for increased interest, increased attention to, and respect for, detail, and the availability of a fund of information, all too often lost because it has not been asked for.

As the present trial was half-way completed, Professor Hogben was good enough to show us the manuscript of his joint paper (Hogben and Sim, 1953), which has since appeared. This account of a simple experiment in human pharmacology admirably summarizes all salient features of this type of trial, and we commend it to all interested.

Summary

The effect of chlorpromazine was studied in 27 chronic agitated psychotic patients. Of these, 13 were schizophrenics, 11 belonged to the affective group, and 3 to the senile group. The patients were used as their own controls, chlorpromazine and identical inert placebo tablets being alternated in the same patient over varying periods. Records were kept independently by the medical and day and night nursing staff. The code of the trial was known to only one of those taking part in it, and assessment was based on the retrospective examination of the records of each patient.

Seven patients were considered definitely and 11 slightly improved. Improvement often did not become apparent until after three to six weeks of continuous medication (at or around the level of 150 mg. a day). The affective group appeared to respond slightly better than the schizophrenics. The patients became quieter, less tense, and less disturbed by their hallucinations and delusions, and more amenable to the suggestions and care of the nursing staff. Three patients were thought fit for parole, though none were thought fit for discharge.

Nine patients showed an increase in weight ranging from 11 to 34 lb. (5 to 15.4 kg.) in 22 weeks. All were members of the definitely or slightly improved group. This increase probably reflects improved eating habit.

One case developed transient jaundice, and two cases showed slight and transient blood changes. Apart from this the drug appeared to be tolerated well in the dosage ultimately adopted (150 mg. a day). None of the patients required extra sedation when on chlorpromazine.

It is concluded that this drug may have its place in the management of the chronically overactive psychotic patient, and that controlled trial in other psychiatric conditions is called for.

We wish to express our thanks to Dr. J. J. O'Reilly, physician-superintendent of Winson Green Hospital, for facilities generously put at our disposal at that hospital; to Drs. A. B. Hegarty, P. M. Jeavons, E. Jacoby, and C. MacDermott, and the day and night nursing staff of the hospital for taking part in the assessment of results; to Dr. W. R. Thrower, of Messrs. May and Baker, Ltd., for advice and a liberal supply of chlorpromazine and placebo tablets; and to the Birmingham Regional Hospital Board and the United Birmingham Hospitals Endowment Fund for financial support.

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CHLORPROMAZINE AND INSULIN IN PSYCHIATRY

BY

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Chlorpromazine hydrochloride is a phenothiazine derivative with a chemical structure resembling many of the antihistamine drugs. It has not itself, however, pronounced antihistamine effects (Courvoisier *et al.*, 1953), but has some hypotensive (Courvoisier *et al.*, 1953) and well-established anti-emetic (Rouchy, 1952; Friend and Cummins, 1953) and hypothermic (Laborit and Huguenard, 1951; Dundee *et al.*, 1953) properties. The use of this drug in psychiatry has largely been studied by French workers (Hamon *et al.*, 1952; Delay and Deniker, 1953), and it has been described as useful in states of excitement and anxiety, and as a potentiating drug in continuous narcosis.

Insulin is well known for its use in psychiatry, and the work following its introduction by Sakel (1935) and its use in modified form by Sargant and Craske (1941) is well reviewed by Kalinowsky and Hoch (1952).

Indications for Present Study

An anxiety state consists of a multitude of somatic and mental symptoms brought about by a previously conditioned fear reaction. The study of psychoneurosis with anxiety symptoms is difficult because these symptoms are produced only in emotion-laden situations, and a careful control of these situations is not usually practicable.

It is possible, by producing hypoglycaemia with small doses of insulin, to produce artificially a condition which has similar symptoms to the naturally occurring anxiety state though differing in the initial mode of production. This modified anxiety state is easily controlled by the dosage of insulin, and it provides an excellent situation whereby the symptomatic "anti-anxiety" effect of a drug such as chlorpromazine can be tested.

One source of error which needed to be eliminated in this study was the possibility of chlorpromazine altering the sensitivity of the body to insulin and hence affecting the hypoglycaemia which in turn induced the anxiety state. Previous studies of the action of this drug had shown some slight lowering of blood sugar in dogs (Courvoisier *et al.*, 1953) but no effect on adrenaline-induced hyperglycaemia. To exclude the possibility of this error an insulin-sensitivity test was performed and then compared with a similar test after the administration of chlorpromazine. It was also desirable to know if combinations of insulin and chlorpromazine had any advantage over insulin and chlorpromazine used separately, as a means of therapy in psychiatric states.

The aims of the present study were to ascertain (1) the effect of chlorpromazine on the "anxiety state" produced by insulin-induced hypoglycaemia; (2) the effect of chlorpromazine on fasting blood sugar and on the insulin sensitivity of the patient; and (3) the usefulness of chlorpromazine combined with insulin as a form of therapy.

Details of Investigation

1. (*a*) Eleven patients aged 17 to 38 years (average 26 years) were given, before breakfast on successive days, subcutaneous soluble insulin in doses of 5, 10, 20, 40, and 60 units. The following signs and symptoms were recorded at 30-minute intervals for a total period of two and a half hours after the injection: palpitation, tachycardia, perspiration, flushing, anxiety, restlessness, epigastric sensation, tremor. The following grading was used to record each symptom: nil −; slight +; marked ++; extreme +++. The total number of + given to each patient for a particular dose of insulin was noted and termed the "anxiety quotient." An example is shown in the Table. The anxiety quotients of the five insulin tests for each patient were totalled and known as the total anxiety quotient for that particular patient. The average of the total anxiety quotients for the 11 patients was then determined and known as the mean total anxiety quotient. (*b*) Chlorpromazine, 50 mg. orally thrice daily, was then given for four days in order to establish any cumulative effects, and at 9 a.m. on the morning of the test 100 mg. of chlorpromazine was given, and at 9.30 a.m. the insulin was injected subcutaneously, the anxiety quotient again being determined. This was performed for 5, 10, 20, 40, and 60 units of insulin as before. (*c*) The mean total anxiety quotients before and after chlorpromazine were compared, and a statistical comparison was made to determine if the chlorpromazine had any significant effect in controlling the anxiety symptoms.

Patient with 40 units of Insulin at 9.30 a.m., Chlorpromazine Nil

	9.30 a.m.	10 a.m.	10.30 a.m.	11 a.m.	11.30 a.m.	12 noon
Palpitation	−	−	+	+	+	−
Perspiration	−	+	+	+	++	+
Anxiety	−	−	−	+	−	−
Epigastric sensations	−	−	−	−	−	−
Restlessness	−	−	+	+	+	−
Tachycardia (pulse)	−(60)	−(64)	+(72)	+(74)	−(66)	−(64)
Tremor	−	−	−	+	+	+
Flushing	−	−	−	−	−	−

Anxiety quotient = 18.

2. Blood-sugar estimations were performed on venous blood when fasting, and then at intervals of 30 minutes for two and a half hours after the injection of 1½ units of insulin intravenously at 9.30 a.m. This was done for each patient both before and after chlorpromazine administration (50 mg. thrice daily, with 100 mg. at 9 a.m. on the day of the test). The fasting blood sugar, the blood-sugar fall 30 minutes after insulin, and the average level of blood sugar at half-hourly intervals for two and a half hours after insulin were compared both before and after chlorpromazine.

3. Besides the 11 patients given insulin alone, chlorpromazine alone, and insulin and chlorpromazine combined, another group of 12 excited refractory patients were given chlorpromazine, 150 mg. daily, and their symptoms and ward management compared with their condition when they were given 100 mg. of chlorpromazine orally plus 20 units of insulin subcutaneously in the morning and 50 mg. of chlorpromazine after lunch.

Results

Effect of Chlorpromazine on Insulin-induced Anxiety Symptoms

(*a*) Total Symptoms:

The mean total anxiety quotient for each patient who had undergone a total of five insulin tests = 35; standard deviation = 15.8.

After chlorpromazine the mean for the same patients with the same doses of insulin = 27.9; standard deviation = 12.2.

The total number of patients = 11.

Variance ratio: F = 1.7 (not significant at 5% level).

Student's t = 1.8: for 10 degrees of freedom this does not reach the 5% probability level and is not significant.

(*b*) Palpitation and Tachycardia:

Insulin alone: mean total = 9.5; standard deviation = 5.3.

Insulin + chlorpromazine: mean total = 13.5; standard deviation = 5.0.

Variance ratio = F = 1.1 (not significant at 5% level).

Student's t = 2.5: for 10 degrees of freedom this reaches the 5% probability level and is probably significant.

(*c*) Perspiration, Flushing, Restlessness, Anxiety, Tremor, and Epigastric Sensations:

Insulin alone: mean total = 25.5; standard deviation = 14.0.

Insulin + chlorpromazine: mean total = 14.4; standard deviation = 10.2.

Variance ratio: F = 1.9 (not significant at 5% level).

Student's t = 3.4: for 10 degrees of freedom this reaches the 1% probability level and is therefore significant.

Therefore chlorpromazine acts on the insulin-induced anxiety state with: (*a*) some apparent but not significant decrease in total symptoms; (*b*) some increase in palpitation and tachycardia; and (*c*) marked decrease in perspiration, flushing, restlessness, anxiety, epigastric sensation, and tremor.

Effect of Chlorpromazine on Fasting Blood Sugar and the Insulin Sensitivity of the Patient

(*a*) Mean Fasting Blood-sugar Levels:

Patients not treated with chlorpromazine = 79 mg. per 100 ml.; standard deviation = 13.9.

Patients treated with chlorpromazine = 73 mg. per 100 ml.; standard deviation(s) = 13.0.

The total number of patients = 19.

Variance ratio: F = 1.1 (not significant at 5% level).

Student's t = 2.0: for 18 degrees of freedom this has no statistical significance.

Therefore chlorpromazine causes some apparent lowering of the fasting blood sugar, but this is not significant.

(*b*) Mean blood-sugar level half an hour after giving insulin, 1½ units, intravenously:

Patients not given chlorpromazine = 56 mg. per 100 ml. (that is, fall in level of (79 − 56) = 23 mg. per 100 ml.)

Patients given chlorpromazine = 49 mg. per 100 ml. (that is, fall in level of (73 − 49) = 24 mg. per 100 ml.)

Therefore chlorpromazine has no significant effect on the immediate fall of blood sugar following a dose of insulin.

(*c*) The mean blood sugar at half-hourly intervals for two and a half hours after insulin, 1½ units, has been given:

Patients not given chlorpromazine = blood sugar mean was 67 and fell 79 − 67 = 12 mg. per 100 ml.

Patients given chlorpromazine = blood sugar mean was 62 and fell 73 − 62 = 11 mg. per 100 ml.

Therefore chlorpromazine has no significant effect on the prolonged fall of blood sugar following a dose of insulin.

Therefore chlorpromazine has no significant effect on fasting blood-sugar level (slight hypoglycaemic effects may later be revealed on a large-scale investigation), on immediate fall in blood-sugar level following a dose of insulin, or on prolonged fall in blood-sugar level following a dose of insulin.

Combined Effects

The combination of insulin with chlorpromazine had a marked effect both on the subjective feelings and on the behaviour of the patient. Subjectively, the patient experienced migrainous headaches, dizziness, palpitation, and drowsiness, but no spontaneous complaint was made of these symptoms during the hours of treatment—that is, 9.30 a.m. to 12.30 p.m. These symptoms could be elicited either by direct questioning during the treatment or else the patient would mention them spontaneously later in the day after the effects of the drugs had diminished.

The behaviour of the patients followed a definite pattern and they became motionless, drowsy, and relaxed. This state appeared to be very similar to that which can be produced by light hypnosis. The excited refractory patients were appreciably calmer and more manageable when on combined insulin and chlorpromazine than when on chlorpromazine alone. Feeding difficulties and the loss of weight, neither of which had been relieved by the chlorpromazine alone, disappeared with the combination.

No evidence of any liver damage was obtained with the patients on the combination, though a transient jaundice, which faded when the drug was stopped, appeared in one of the patients on chlorpromazine alone. There was no evidence of chlorpromazine decreasing the predisposition to epileptic fits which sometimes occurs with hypoglycaemia. In fact, the clinical impression was of some slight increase in this tendency.

Conclusion

Chlorpromazine did not influence the action of insulin on blood-sugar levels. There was slight apparent lowering of fasting blood-sugar levels, but this was not statistically significant.

Chlorpromazine caused some apparent but not significant decrease in the total number of anxiety symptoms and altered the type of these symptoms. Palpitation and tachycardia were increased. Perspiration, flushing, anxiety, restlessness, epigastric sensations, and tremor were diminished.

Insulin and chlorpromazine combinations were useful in controlling refractory excited patients who were not controlled by either chlorpromazine or insulin alone in the above dosage.

The combination was also useful in making more manageable patients who became excited during insulin coma treatment. When chlorpromazine (100 mg. orally) was given along with the insulin and (50 mg.) later in the day, there was such a marked diminution in restlessness and excitement that schizophrenic patients who were previously unmanageable and had to have their treatment discontinued were enabled to be given a full course of comas. No difficulty was experienced in terminating the comas by the usual methods, and doses of insulin up to 670 units have been used in combination with the chlorpromazine.

Owing to the possibility of the lethargic, stuporous state deepening into hypoglycaemic coma, adequate nursing supervision and arrangements for giving emergency glucose are needed.

One complication of chlorpromazine is liver damage (Lehmann and Hanrahan, 1954). The insulin should help to protect damage of the liver by promoting glycogenesis.

The comments of one of the patients on chlorpromazine, 100 mg. at 9 a.m., and insulin, 20 units at 9.30 a.m., are worth recording. "I haven't noticed very much difference. I got throbbing headaches about 10.30 a.m. and palpitations about 11 a.m. When I had been on tablets (chlorpromazine) alone my legs felt weak. On injections (insulin) and tablets (chlorpromazine) I felt tired and wanted to sleep. Sleep was not thoroughly deep because my mind was still on the turn. Time passed quickly. Directly after the treatment (12 a.m.), for two hours I felt very confident. I could go to the canteen without the feeling that people were looking at me. It was a beautiful feeling—just the opposite feeling to what I usually get. The confident feeling wears off, and by tea-time I am wary. I wonder whether to chat at table or to say nothing. At lunch I can eat a lot and make a pig of myself and not care. At tea it is different, and I am self-conscious again. The treatment has not eradicated anything from my mind. I know it is still up to me to face my difficulties."

Summary

A total of 31 patients were given combinations of chlorpromazine and insulin. The blood-sugar levels in 19 patients and the symptoms induced by insulin in 11 patients were compared both before and after chlorpromazine had been given.

The effect of insulin and chlorpromazine combined as a means of therapy was compared with the effect of each of these compounds used separately.

We thank Dr. Isaac Frost for his co-operation in allowing part of the investigation to be carried out in his wards.

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AIR POLLUTION AND BRONCHITIS

BY

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The crude death rate from bronchitis shows a steady and marked increase in passing from rural areas to the towns, cities, and conurbations (Table I). Attention has recently been directed to air pollution as a possible

TABLE I.—*Death Rates from Bronchitis (International List Nos. 500–502) Per 100,000 Living, by Population Density, England and Wales*, 1951

		Rural Areas	Urban Areas			Conurbations
			Less than 50,000	50,000 to 99,999	100,000 and over	
Population (thousands) ..	M.	4,276	4,477	1,583	2,761	7,952
	F.	4,166	4,868	1,753	3,030	8,934
Bronchitis death rates per 100,000	M.	69·4	98·5	100	117·8	132·1
	F.	47·3	56·0	58·5	64·9	73·7

cause for some of these differences, and the great increase in deaths, most notably from bronchitis, which occurred during and immediately after a prolonged smoke fog in London in 1952 (Logan, 1953) has added

weight to this hypothesis. The fatal effects of severe smoke fogs have been described on several previous occasions (Marsh, 1948; Schrenk *et al.*, 1949; Logan, 1949; County M.O.H. for London, 1952). The victims are usually, though not invariably, adults in the latter half of life or sufferers from chronic respiratory disease. The illness from which they die appears typically to be in the nature of an acute suffocative bronchiolitis.

We do not know to what extent, if at all, air pollution of a lesser degree than that which causes these dramatic episodes is harmful to health. One way of examining this question is to see to what extent death rates vary with the average air pollution in different localities. An attempt has been made to do this for the county boroughs of England and Wales for bronchitis in relation to air pollution with sulphur dioxide and with solid matter. Sulphur dioxide has fallen under suspicion because it has been shown in the laboratory to have effects on human respiratory function in concentrations met with in smoke fogs; Amdur *et al.* (1953) found that the inhalation of sulphur dioxide in concentrations of 1–8 p.p.m. increased the pulse and respiratory rates in normal human volunteers and caused the respiration to become more shallow. Cralley (1942) showed that sulphur dioxide in concentrations somewhat higher than those encountered in smoke fogs inhibited ciliary activity in the human trachea.

Present Investigation

Two age groups were selected for this study, 45–64 and 65+, as it is at these ages that bronchitis is commonest and susceptibility to smoke fogs greatest. The numbers of deaths and the populations at these ages were obtained from the Registrar-General's Annual Review and the 1951 census

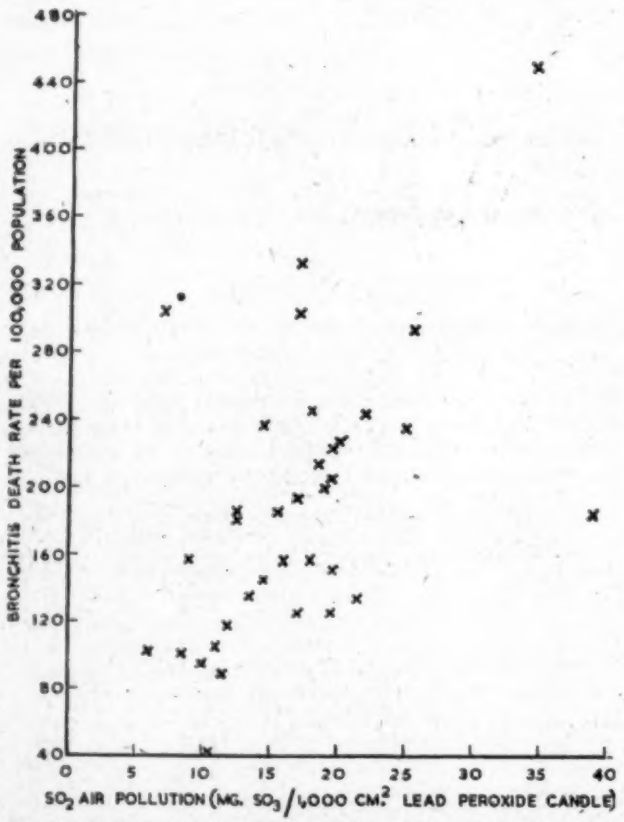

FIG. 1.—Relationship between bronchitis death rates in 35 county boroughs and mean sulphur dioxide air pollution. Men aged 45–64, 1951. Correlation coefficient=0.5076. Significant between 0.1 and 1%.

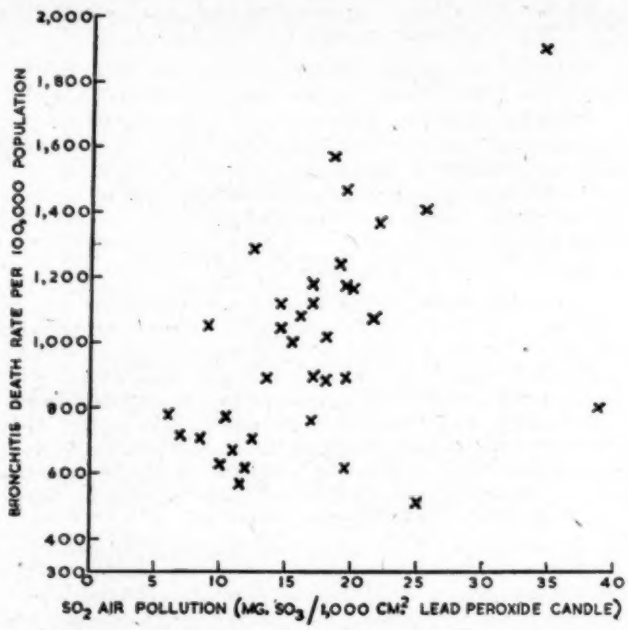

FIG. 2.—Relationship between bronchitis death rates in 35 county boroughs and mean sulphur dioxide air pollution. Men aged 65+, 1951. Correlation coefficient=0.4443. Significant between 1 and 2%.

1% sample respectively. From these figures the bronchitis death rates in the different county boroughs were calculated. The air pollution records were taken from the atmospheric pollution bulletins published monthly by the Department of Scientific and Industrial Research. All the county boroughs in England and Wales making returns of monthly readings from two or more stations (lead peroxide candle method) were used.

The existing air pollution data when used as a measure of the quality of the air inhaled by the population of a county borough suffers from certain deficiencies. Stations have not always been sited to record average conditions, but have sometimes been placed in specially chosen situations in order to pin-point a particularly bad area. Prevailing winds and geographical configurations influence the readings, and the number of stations in proportion to population varies from one county borough to another.

In the first instance, the mean of the maximum monthly readings (amongst the different stations) for each county borough was used as a yearly index. Later it was found that a similar result was obtained if all the stations in each county borough were included in calculating the mean annual figure. The latter was then adopted as the index. Scatter diagrams relating the death rates from bronchitis to the mean annual sulphur dioxide pollution figure were constructed for men and women in the two age groups (45–64 and 65+) for the years 1950, 1951, and 1952—that is, for the census year and the years on either side of it. Figs. 1 and 2 show the diagrams for the men for 1951 and illustrate the relationship between bronchitis death rates and sulphur dioxide pollution that was found to occur in both male age groups for all three years. Correlation co-efficients were calculated. In the men there was a moderate degree of correlation in each case, and the likelihood that this association was due to chance varied from 1 in 50 to 1 in 1,000 (Table II). In the women, on the other hand, in only two out of the six sets of data was there a significant association—namely, in women over 65 for the two years 1951 and 1952.

Although there is a significant statistical association between bronchitis death rates in men over the age of 45 and sulphur dioxide pollution, it is clear that this association might be due to both variables being directly related to a third variable or group of variables. The possibility that immediately springs to mind is that both might be related

TABLE II.—*Correlation Coefficients Between SO_2 Air Pollution and Bronchitis Death Rates in 33–35 County Boroughs*

Age	1950			1951			1952		
	r	No.	Probability	r	No.	Probability	r	No.	Probability
Men:									
45–64	0·5478	33	Sig. 0·1 to 1%	0·5076	35	Sig. 1 to 2%	0·4613	35	Sig. 0·1 to 1%
65+	0·4513	33	Sig. 0·1 to 1%	0·4443	35	Sig. 1 to 2%	0·4095	35	Sig. 1 to 2%
Women:									
45–64	0·2732	33	Not sig.	0·2763	34	Not sig.	0·2932	34	Not sig.
65+	0·3378	33	,,	0·4279	35	Sig. 1 to 2%	0·6223	35	Sig. 0·1%

to the complex of general social conditions or to some component of it. Indeed, the Registrar-General's Decennial Supplements (1938, 1954) show clearly that in both sexes there is a strong relationship between the standardized mortality ratio for bronchitis and social class as defined on an occupational classification. If sulphur dioxide air pollution showed a similar relationship to general social conditions, then the significance of the association between bronchitis deaths and sulphur dioxide pollution would be reduced.

This possibility was tested by using two separate indices of social conditions and relating them to the mean sulphur dioxide pollution figures. The first index was the average number of persons per room in the different county boroughs as given in the 1951 census 1% sample report (Registrar-General, 1952), and the second was a social class of towns scale devised by Wilkins (1952) and based on the estimated percentage of households in which the chief wage earner's basic weekly wage rate equalled or exceeded £7 10s. The same county boroughs were used in all three cases.

The correlation coefficient between persons per room and sulphur dioxide air pollution was −0.1538 and between the income classification and sulphur dioxide pollution −0.2478. In neither case was this slight degree of association statistically significant.

Bronchitis and Other Pollutants

It seemed possible that bronchitis death rates might be related not specifically to sulphur dioxide pollution but to some other pollutant, the amount of which in the air varied with the amount of sulphur dioxide, or to a combination of pollutants.

The Committee on Air Pollution (1953) estimated the amount of the chief pollutants discharged annually in Great Britain as follows:

Smoke	2.1	million tons
Grit	0.6	,, ,,
Sulphur dioxide	5.3	,, ,,
Other acids (nitric and hydrochloric)	0.3	,, ,,
Carbon monoxide	24.0	,, ,,

Most of the pollution stations record total solid matter deposited in addition to sulphur dioxide. The same procedure was adopted as in the case of sulphur dioxide to see if there was any statistical relationship between bronchitis death rates and solid matter pollution. Table III shows that

TABLE III.—*Correlation Coefficients Between "Total Solids" Air Pollution and Bronchitis Death Rates in 33–42 County Boroughs*

Age	1950			1951			1952		
	r	No.	Probability	r	No.	Probability	r	No.	Probability
Men:									
45–64	0·1727	40	Not sig.	0·4568	42	Sig. 0·1 to 1%	0·5439	33	Sig. 0·1 to 1%
65+	0·2387	40	,,	0·1863	42	Not sig.	0·5724	33	Sig. 0·1%
Women:									
45–64	0·2597	40	,,	0·2232	42	,,	0·3220	33	Sig. 5%
65+	0·1299	40	,,	0·1664	42	,,	0·4601	33	Sig. 0·1 to 1%

there was a significant association between death rates from bronchitis and solid matter pollution for both sexes and in both age groups selected for 1952. However, in the eight sets of data relating to 1950 and 1951 only in one case (men aged 45–64, 1951) was there a significant association. It would appear, therefore, that there is a much stronger association between bronchitis mortality rates and sulphur dioxide pollution than there is between the former and air pollution with solid matter.

Discussion

It is difficult to draw any very firm conclusions based on the statistical approach because of the imperfections of the basic data. Bronchitis is a disease which, although very commonly diagnosed, is still not well defined or understood. The pollution records are unsatisfactory, as we cannot be confident, for the reasons given above, that they give a fair estimate of the amount of pollutants actually inhaled by the populations concerned. However, the consistency of the relationship between mean sulphur dioxide pollution and bronchitis death rates in the county boroughs does strongly suggest that whatever other factors may be involved sulphur dioxide pollution plays some part in causing death from bronchitis. From the limited data examined it would seem to be more important in this respect than pollution of the air with solid matter.

The general poverty complex has been shown to be of basic importance in determining the death rate from bronchitis (Registrar-General, 1938, 1954), but it appears from the calculations which have been made that air pollution can be separated from these as a distinct aetiological factor. W. Roe and R. Wrighton (1952, unpublished communication), using an index of social conditions in the county boroughs devised by Buckatzsch (1946), found that there was no relationship between bronchitis death rates and air pollution at ages under 15. The most likely hypothesis would seem to be that air pollution is not a prime aetiological factor in bronchitis but that it acts as a secondary or aggravating factor, and that on certain occasions, as in a prolonged smoke fog, it can have a fatal effect on those who are subject to this disease.

Much further research is required to establish the exact part that air pollution plays in the causation and aggravation of respiratory disease. In particular, morbidity studies are required in which the incidence of bronchitis and its exacerbations are studied in relation to variations in meteorological and pollution conditions.

Summary

A significant correlation has been found between the average sulphur dioxide air pollution in the county boroughs of England and Wales and the mortality rates for bronchitis in men aged 45 and over, for the three years 1950, 1951, and 1952. In only two of six sets of data was a similar association found for women at the same ages.

The association between air pollution with solid matter and bronchitis mortality rates was much less consistent. Only three of the six sets of data in the case of men and two in the case of women were significant.

There was no significant association between average sulphur dioxide pollution and two indices of general social conditions. The latter consisted of one based on income and one on housing conditions. The evidence supports the hypothesis that sulphur dioxide air pollution is a factor in determining the magnitude of the bronchitis death rate of middle-aged and elderly males.

Miss Audrey Hutcheson carried out the computations and prepared the diagrams for this study.

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THE COLLAGENOUS CHANGES IN THE INTERVERTEBRAL DISK WITH AGE AND THEIR EFFECT ON ITS ELASTICITY

AN X-RAY CRYSTALLOGRAPHIC STUDY

BY

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The histological changes in the structure of the intervertebral disk throughout life have been well described by Coventry, Ghormley, and Kernohan (1945). These indicate that an integration process occurs during the first and second decades of life, but that in the third decade evidence of degenerative change appears. Little attention has been paid to the collagenous structure in the disk, and our work has been directed to this in an endeavour to elucidate changes in the collagen/mucopolysaccharide complex in the disk. The bearing of this work upon the aetiology of disk herniation is being studied at the present time and will be described in a later publication.

Our studies were made on fresh human intervertebral disks removed at operation or necropsy, using an *x*-ray spectrometer with a comparatively high intensity *x*-ray beam. This allowed *x*-ray diffraction photographs of the specimens excised from the disks to be examined rapidly, so that little change in the structure of the material was possible during the exposure of approximately half an hour.

Experiments with Air-dried Specimens

The annulus fibrosus was peeled from the disk and cut into long strips which could be held in the clamps of a stretching frame for the investigation of the elasticity of the disk wall. The specimens of both nucleus and annulus were allowed to dry for ten hours to eliminate most of the unbound water, which, if present, produces an intense diffuse ring on the *x*-ray diffraction photographs of the material and so masks, to some extent, the *x*-ray diagram of the collagen or collagen/polysaccharide complex. If this process was allowed to continue too long, irreversible changes appeared in the structure of the collagen of the disk. In particular, specimens allowed to stand over several days showed changes in orientation, and the original structure could not be restored on wetting the sample again. Thus we think the specimens examined had a uniform moisture content during the course of the examination, and changes in crystallinity and orientation of the collagen were definitely related to the conditions of the material *in vivo*.

Our later experiments were made using a modified technique in that the disk was frozen and thin sections were then cut and mounted in the *x*-ray spectrometer. By this means the samples retained their swollen condition, as little water was dried out during the examination.

The collagen of the rat-tail tendon was used for comparison, and the following effect on its *x*-ray diagram was found on stretching: (*a*) increase in orientation of the fibrils, and (*b*) a reversible increase in the spacings associated with distances along the fibre axis comparable to the lattice extension of α keratin before the main $\alpha \rightarrow \beta$ transformation occurs (Table I).

TABLE I.—*Reflections in X-ray Diagram of Rat-tail Tendon*

Equatorial Reflections		Meridional Reflections		Other Reflections	
Unstretched	Stretched	Unstretched	Stretched	Unstretched	Stretched
11·8 Å 5·7 Å 4·6 Å	11·8 Å 5·7 Å 4·6 Å	2·86 Å 3·95 Å	2·95 Å 4·04 Å	7·2 Å	7·4 Å

A. Nuclear Changes with Age

Many specimens from subjects whose ages ranged from 3 weeks to 79 years were examined. The results of the *x*-ray diagrams are summarized in Table II (see Figs. 1–3).

The equatorial reflection at 11.8Å is associated with the side-chain spacing—that is, the average distance between the chains. It can be seen that this remains approximately constant in the air-dried specimens first investigated, except in those of an early age in which the reflection was absent.

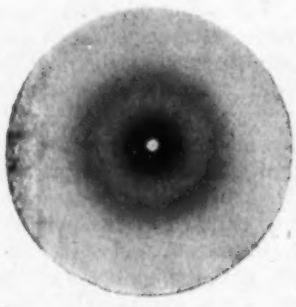

FIG. 1

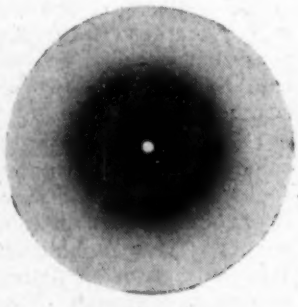

FIG. 2

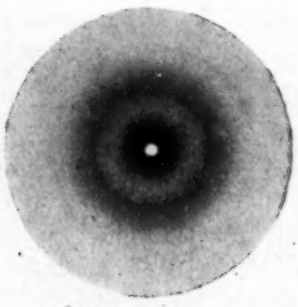

FIG. 3

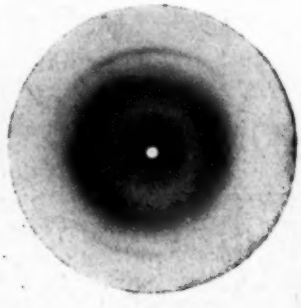

FIG. 4

FIG. 1.—Nucleus pulposus. Age 3 weeks (*x*-ray beam parallel to spinal axis). FIG. 2.—Nucleus pulposus. Age 48 years (*x*-ray beam parallel to spinal axis). FIG. 3.—Nucleus pulposus. Age 70 years (*x*-ray beam parallel to spinal axis). FIG. 4.—Annulus fibrosus. Age 24 years (*x*-ray beam parallel to radial direction of disk).

This, coupled with the fact that the 2.85Å spacing is most probably associated with the amino-acid repeat distance along the fibre axis, would suggest that the gels of the nucleus pulposus are made up of aligned collagen molecules separated by a distance much greater than the normal 11.8Å. This structure is probably a collagen/polysaccharide/water system giving a deformable gel in which the structure is retained by the aligned but widely separated collagen chains of the complex. The 2Å reflection is more difficult to identify, the two possibilities which seem most feasible being that it is either (*a*) the second order of ~ 4Å polar arc of the standard collagen diagram, or (*b*) a reflection due to sodium chloride. More information is required before any definite conclusions can be formed, and this aspect is being investigated.

The other spacings shown in Table II seem to agree with those found for the rat-tail tendon, but it is difficult to identify them with any specific measurement in the same manner as those of the 11.8Å and 2.85Å spacings, except for the 4.7Å reflection, which would appear to be due to a disorientated β structure superimposed on that of the orientated collagen. In the freeze-dried specimens there is an increase from 11.8Å to a minimum of 14.5Å in the side-chain spacing. A careful study of the spreading of these arcs on the *x*-ray diagram would suggest a mean separation of chains of about 20–30Å. It is interesting to note this agreement with the measurements of the pore-size given by Sylvén *et al.* (1951) in their electron microscope studies of the nucleus pulposus.

It can be seen from the results recorded that with advancing age the collagen of the nucleus pulposus becomes more orientated and a degenerative process is at play until the stage of crystallization and fibrillation of the collagen is reached in the disks of very old subjects. It is probable that this process occurs in relation to the absorption of mucopolysaccharide from the nucleus. Thus the nucleus loses its gel structure with advancing age. The presence of the disorientated diagram typical of a β protein (identified by a strong ring at 4.7Å and a more diffuse reflection at about 3.9Å in the specimens from subjects aged 70 and 78 years) is significant. It may be due to the denaturation of the folded and soluble proteins into a fully extended form to give a disorientated and tightly hydrogen-bonded β crystalline lattice which would inhibit any elasticity in the nucleus. These diagrams of specimens from subjects aged 70 and 78 suggest, therefore, that the nucleus pulposus is no longer an isotropic medium and cannot be capable of distributing stresses uniformly throughout its structure.

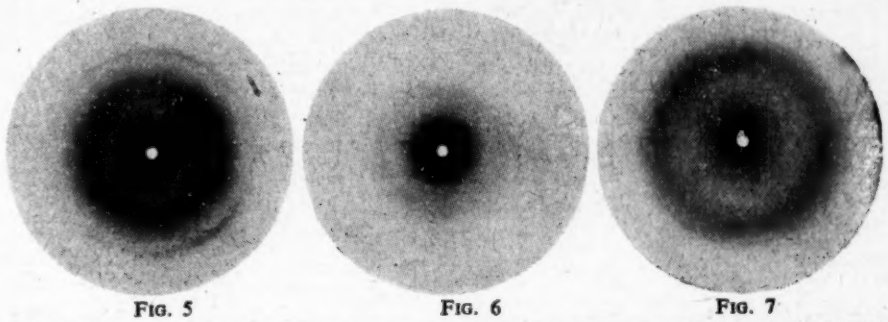

FIG. 5 FIG. 6 FIG. 7

FIG. 5.—Annulus fibrosus. Age 48 years (*x*-ray beam parallel to radial direction of disk).
FIG. 6.—Annulus fibrosus. Age 78 years (*x*-ray beam parallel to radial direction of disk).
FIG. 7.—Annulus fibrosus. Age 45 years (*x*-ray beam parallel to radial direction of disk. Photographs taken immediately after excision from the disk—that is, in a "wet" state).

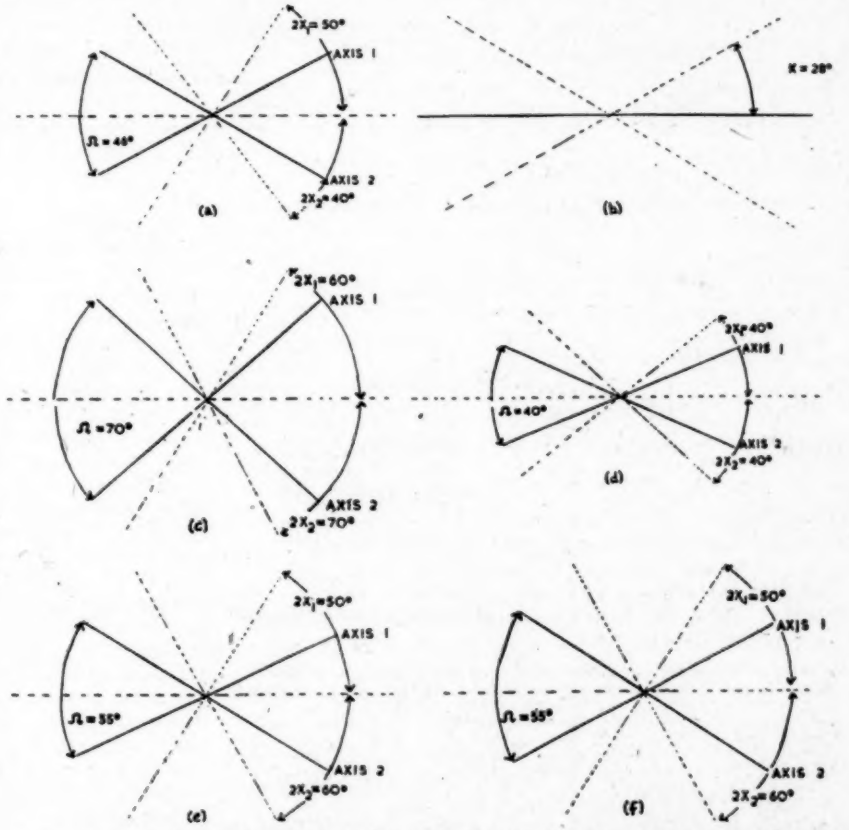

FIG. 8.—Biaxial orientation of annulus fibrosus—dry specimens. (*a*) Aged 44. Beam perpendicular to spinal axis. (*b*) Aged 35. Beam parallel to spinal axis. (*c*) Aged 48. Unstretched. (*d*) Aged 48. Stretched. (*e*) Aged 53. (*f*) Aged 70.

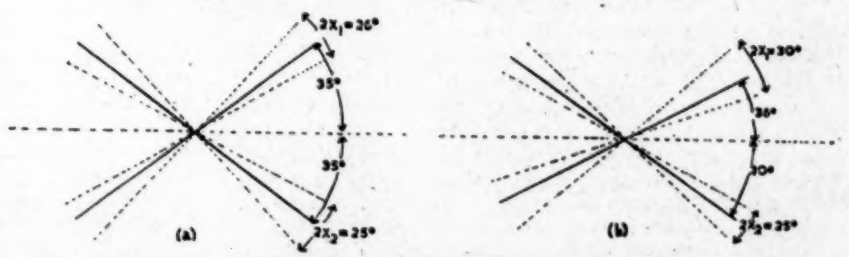

FIG. 9.—Biaxial orientation of annulus fibrosus—wet specimens. (*a*) Aged 45. (*b*) Aged 51.

B. Changes in the Annulus Fibrosus with Age

Table III shows the reflections given by specimens of annulus fibrosus (Figs. 4–7 are representative *x*-ray diagrams).

As the crystallites in the fibrous system such as collagen are in general not parallel, its diffraction picture will not consist of individual spots, but rather of arcs due to the dispersed orientation of the crystallites about an axis. This distortion of the internal structure causes the angular spread

TABLE II

Nucleus Pulposus. Air-dried Specimens

Age	Spacings of Reflections			Remarks
	Equatorial	Meridional	Other Reflections	
3 weeks		2·85 Å	2·0 Å	Completely disorientated. Structure. Side-chain spacing absent
1½ years	11·8 Å	2·85 Å	2·0 Å 3·2 Å 4·3 Å	Still disorientated. 3·2 Å and 4·3 Å are diffuse
2½ „	11·8 Å 4·6 Å	2·85 Å		2·0 Å ring has disappeared. Side-chain spacing at 11·8 Å now resolved
25 years to 28 years. Diagram still disorientated, but shows increasing definition				
48 years	11·8 Å 4·7 Å	2·85 Å 3·20 Å	4·3 Å	Collagen phase well orientated—i.e., becoming crystalline
70 „	11·8 Å 4·7 Å	2·85 Å 3·90 Å		
78 „	11·8 Å 4·7 Å	2·85 Å 3·90 Å		
Newly Excised Freeze-dried Specimens				
51 years	14·5 Å	2·85 Å 4·00 Å		Disorientated liquid phase

TABLE III

Annulus Fibrosus—Air-dried Specimens

Age	Spacings of Annulus Fibrosus			Remarks
	Equatorial	Meridional	Other Reflections	
3 weeks	11·8 Å	2·85 Å		Disorientated structure with other very diffuse reflections
1½ years	11·8 Å	2·85 Å		Still almost completely disorientated
2½ „	11·8 Å	2·85 Å 3·92 Å	4·7 Å	Slight orientation; uniaxial dispersion
From 2½ to 36 years the orientation increases, with the reflections becoming sharper				
44 years	11·8 Å	2·85 Å 3·94 Å	4·7 Å 5·8 Å 7·3 Å	Orientated biaxial structure
48 years to 70 years, the spacings varied only slightly about values given for age 44. The main differences are in the increasing orientation with increase in age. Biaxial dispersed system becoming uniaxial				
78 years				
Freeze-dried Specimens				
45 years	14·5 Å	2·85 Å 4·00 Å	7·0 Å 3·3 Å	Disorientated liquid phase

of the spots, and from the geometry of the diffraction diagram and measurements of this angular spread of the arcs on the *x*-ray diagram the dispersion of the crystallites around the fibre axis can be calculated (Astbury, 1947).

Before the age of 35 years, the crystallites of the collagen of the annulus fibrosus show a uniaxial dispersion, but older specimens show an increasing biaxial character (see Figs. 8 and 9, dispersions shown diagrammatically). With increasing age beyond 48 years, a preferred orientation appears to develop in the biaxial system, so that there is a tendency to revert to the uniaxial fibrillar orientation. *X*-ray photographs of specimens from subjects aged 35 years were taken with the *x*-ray beam parallel to the spinal axis (Fig. 8,b) and perpendicular to the radial direction of the disk. In the latter case the dispersion is approximately twice that of the former. Thus it would appear that the fibrils are laid down in approximately concentric cylinders around the radius in the plane of a cylinder.

Table IV shows the dispersions of the fibres at varying ages.

TABLE IV

Annulus Fibrosus. Air-dried Specimens

Age (Years)	Uniaxial Semi-angle φ	Biaxial		Ω	Remarks
		$2\varphi_1$	$2\varphi_2$		
2½	60°				
35	56°				
35	28°				Beam parallel to spinal axis
44		50°	40°	45°	Approximately equal intensity of arcs
48		60°*	70°	65°	Unstretched (see Fig. 8,c)
48		40°	40°	40°	Stretched approximately 15% (see Fig. 8,a)
53		50°	60°	55°	See Fig. 8,c
67	42°				
70		50°*	60°	55°	See Fig. 8,f
78	45°				
Freeze-dried Specimen					
45		25°	25°	70°	See Fig. 9
51		30°	25°	65°	„ „ 9

φ = Semi-angle of dispersion in uniaxial system. φ_1 and φ_2 = Semi-angles of dispersion about the two axes of the biaxially dispersed system. Ω = Angle between the two axes.

* Arcs of increasing higher intensity with age, showing the development of a preferred orientation and the eventual reversion from the biaxial to a uniaxial system. This change, however, occurs at ages varying between 65 and 75 years.

Discussion

The reversible elasticity of the keratin-epidermin-fibrinogen group of proteins has been shown to be associated (at least in part) with a molecular transformation of the $\alpha \rightleftarrows \beta$ type. It is known that the collagen molecule is an extended form of a particular configuration of the amino-acid residue in the polypeptide chain. Apart, therefore, from a small lattice stretch of about 2%, and at the most 5%, the fibrils of collagen are inextensible. Thus any elongation is clearly connected with the orientation of the collagen fibrils in the wall as shown by the results of the *x*-ray diffraction diagrams of the stretched annulus fibrosus. From the angles of dispersion of the reflections produced before and during stretching of the specimens of annulus fibrosus, it can be seen that elongation is clearly connected with changes in orientation of the collagen fibrils in the wall. Figs. 8,c and 8,d show diagrammatically the effects of stretching upon the disk wall, demonstrating that extension is mainly achieved by alignment of the fibrils—that is, by change of orientation in the wall. A calculation for the case of a specimen from a subject aged 40 years, using the measured dispersions, shows an elongation of about 13% (Happey, Macrae, and Naylor, 1953). This is in reasonable agreement with the measured stretching of the actual specimen (about 15%), and gives an indication of the order of extension which can be obtained by such a source of elasticity. Further, as this extension seems readily reversible, it is reasonable to assume that the increase in orientation of the collagen fibrils is associated with the elasticity of the annulus fibrosus.

It would appear, therefore, that the elasticity and efficient function of an intervertebral disk are dependent upon at least two major factors: (1) The gel properties of the nucleus pulposus. The nucleus should be readily deformed but incompressible, and so convert any vertical pressure into a horizontal and radial thrust on the annulus. A diagrammatic representation of this mechanism is given in Fig. 10. (2) The annulus fibrosus must act as an elastic ring to dissipate the forces applied. This is possible only because of the arrangement of the collagen fibres in their surrounding

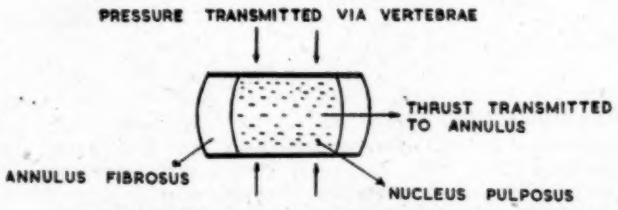

FIG. 10.—Elastic mechanism of the intervertebral disk.

matrix, which is flexible enough to allow the fibrils to show their elasticity due to changes in orientation.

The experiments undertaken show that with advancing age, beginning at the end of the third decade, there are changes in the collagen structure of both nucleus pulposus and annulus fibrosus which affect both factors.

The nucleus loses its gel properties, as seen by the increased orientation and crystallization of the collagen with advancing age, whilst the collagen of annulus fibrosus undergoes similar changes, the fibrils being laid down in a uniaxial arrangement which inhibits its elastic mechanism. In these circumstances the intervertebral disk loses its normal physiological function, with secondary effects upon its associated spinal joints, particularly impaired mobility.

Summary

The collagenous changes in the human intervertebral disks with age have been studied, using *x*-ray crystallographic methods.

The *x*-ray diffraction diagrams so obtained prove that the elasticity of the annulus fibrosus is dependent upon the orientation and mobility of the collagen fibrils, properties which decrease with advancing age after the third decade.

The *x*-ray diffraction diagrams of the nucleus pulposus show that increased orientation and ultimate crystallization of the collagen occurs with advancing age, indicating loss of gel structure and hence impaired elasticity.

The combination of these factors will explain the reduced elasticity of the intervertebral disk with age.

Financial assistance from the Wool Textile Research Council for part of this work is gratefully acknowledged.

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SERUM ANTITHROMBIN CONTENT IN PREGNANCY

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In a follow-up examination of adult cases of coeliac disease the serum antithrombin content estimation was used as a screening test to exclude fibrocystic disease of the pancreas as a possible alternative diagnosis. The results were normal in all cases but one—that of a woman three months gravid. Sera from six other pregnant women were then examined, and since in each case the antithrombin content was found to be much lower than that of normal serum the investigation now reported was undertaken.

Sera were obtained from 120 women whose pregnancy varied from four weeks to full term; from 41 women whose delivery had been from one to twelve weeks previously; from cord blood at 30 births; and from 15 babies aged 1 to 14 days. All pregnancies were normal and the sera were obtained from routine laboratory collections. The babies from whom blood was obtained were likewise normal and full-term. The Table shows the distribution of these sera. The antithrombin content was estimated in every case. The technique

Details of the Sera Examined and the Results Obtained, Expressed as a Percentage of the Normal Mean

Sera	No.	Antithrombin Content			Sera	No.	Antithrombin Content		
		Max.	Min.	Mean			Max.	Min.	Mean
Pregnancy:					Post Partum:				
4– 7 weeks	3	72	60	67	1– 4 weeks	28	62	18	35
8–11 ,,	9	66	26	50	5– 8 ,,	4	106	65	90
12–15 ,,	24	58	22	35	9–12 ,,	9	107	89	100
16–19 ,,	9	45	22	32					
20–23 ,,	10	48	23	34	Total ..	41			
24–27 ,,	11	41	22	33					
28–31 ,,	23	52	22	35	Babies:				
32–35 ,,	11	48	20	36	Cord blood	30	58	20	32
36–39 ,,	16	41	18	29	Newborn				
Full term	4	41	22	32	(1–14 days)	15	64	26	40
Total ..	120								

employed has already been detailed by one of us (MacFarlane, 1952) and is a modification of the original method described by Innerfield *et al.*[1] (1951). Briefly, the test consists of the incubation in a water-bath at 37° C. of a standard solution of thrombin mixed with the serum to be tested, and the timing of the clotting of standard amounts of normal citrated plasma by this thrombin-serum mixture after 5, 10, 15, and 20 minutes' incubation. The clotting times of each sample are expressed as a percentage of those obtained using normal serum as a control, normal and abnormal being tested concurrently.

Results

In the assessment of the results obtained the percentages of the normal of the 20-minute sample of the thrombin-serum mixture only are considered, for in this sample any deviation from the normal is most marked. We have used the same technique over a period of more than two years: the variation in clotting time of some 800 "normal" sera in this 20-minute sample was from 90 to 110% of the mean of each batch of normals tested, and we have come to regard any figure of less than 80% as being pathological. The Chart shows the scatter of the results obtained on examination of the 120 sera taken during pregnancy and of the 41 sera obtained post partum, while the Table also lists the highest, lowest, and mean result obtained in each four-weeks period. It will be seen that from the fourth week of pregnancy onwards the serum antithrombin content is reduced to an abnormal degree. The mean of the three sera tested in the fourth to seventh week of pregnancy is 67%; that of the nine sera in the eighth to eleventh week is 50%; and the means of the sera belonging to the succeeding four-weeks periods to full term all lie around 35% of normal. After delivery the antithrombin content remains low for several weeks, certainly for as long as four weeks, for the highest figure of this group of 28 sera was 62%, with a mean of 35%. Somewhere between five and eight weeks post partum the results return to normal in the majority of cases, three of the four sera in this period tested being normal, while from the ninth week onwards all nine sera tested gave normal results.

All 30 sera obtained from cord blood gave abnormally low results, varying from 20 to 58% of normal, with a mean of 32%. The sera of the babies 1 to 14 days old also showed an antithrombin content much lower than that of normal serum, the mean here being 40%. In the routine investigation to exclude fibrocystic disease of the pancreas the antithrombin content has been within the normal limits in the serum of all the 2-months-old normal babies tested.

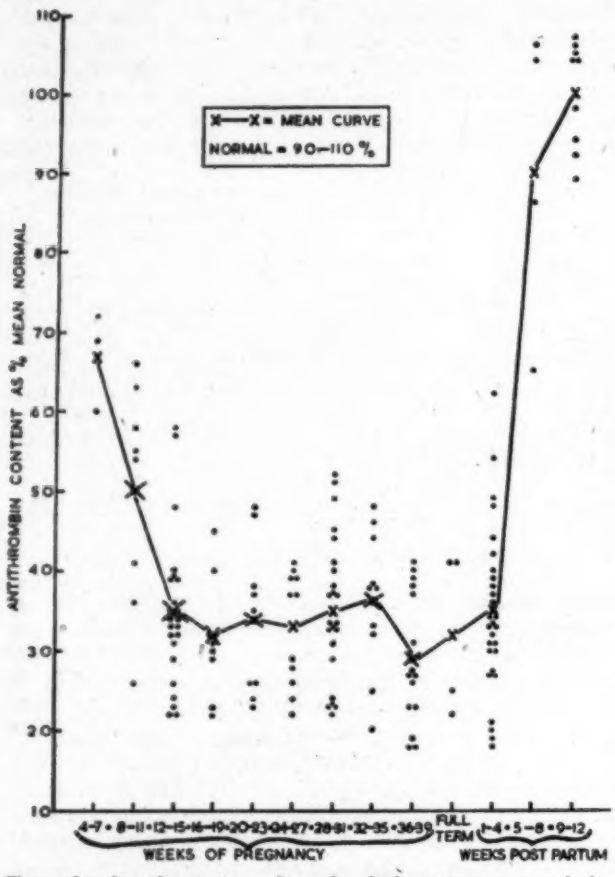

Chart showing the scatter of results during pregnancy and the post-partum period.

These results are included, although they have no direct bearing on pregnancy, because they are interesting, and because they may throw some light on the possible explanation of the low antithrombin levels found in pregnancy. Obviously more investigation of the sera of the newborn is necessary.

Discussion

The results seem to indicate that the serum antithrombin titre offers a simple and reliable aid to the diagnosis of pregnancy in difficult cases, probably from as early as the fourth week, and certainly from the eighth week onwards. It is not in any way suggested that this test should supplant the well-proved animal tests in present routine use, though it seems to have certain advantages. In the investigation of uterine bleeding following amenorrhoea it might be of considerable assistance, however, for, whereas the biological tests give normal results very rapidly after abortion or miscarriage, the results here recorded indicate that the antithrombin content of the serum may remain low for several weeks following such an occurrence.

The test is easily executed, requires no complicated apparatus or reagents, and can be carried out on blood obtained from a finger-prick, for the test employs only 0.1 ml. of serum. It must be emphasized that it is essential to compare the serum to be tested with at least one normal control, tested concurrently, for, as has been stressed by MacFarlane, no absolute comparison is possible for technical reasons between the results obtained in one batch and those obtained in another.

The examination of more than 800 "normal" sera while investigating the results in fibrocystic disease of the pancreas has given only six "false-positive" results. These six patients suffered from chronic eczema, miliary tuberculosis, and acute exacerbations of chronic respiratory disease (four cases). The error in normal sera is therefore apparently less than 1%, and even the "errors" occurred in patients quite obviously ill. It is interesting to note in passing that the results obtained from the five cases of respiratory disease became normal within four to eight weeks of the response of the complaint to treatment. Similarly, too, in the three cases of acute pancreatitis investigated, in which the patients recovered following operation, the low levels encountered at the onset of the disease returned to normal seven, nine, and thirteen weeks respectively after operation. Otherwise fibrocystic disease of the pancreas was the only condition found in which the antithrombin level of the serum was low. In children with this disease a lowered serum content was found in 106 of the 118 proved cases investigated; in this condition the level remains low despite treatment.

It would be pleasant to be able to offer some definite rationale for these results, in pregnancy as in the other conditions in which a low titre was found. To exclude a simple hormonal change in pregnancy the sera from eight female laboratory technicians were examined weekly for a period of ten weeks. The results all lay within normal limits and the menstrual cycle produced no variations in any case. A specious theory regarding the cause of the low levels found in fibrocystic disease of the pancreas and acute pancreatitis could be based on the simple fact that the addition of a minute amount of crude trypsin (as a high dilution of liq. trypsin co.) to normal serum produces a very low antithrombin titre in the normal serum. In both these conditions it is possible that there is an excess of trypsin in the blood, this excess producing the lowering of the antithrombin content of the serum. It might be suggested that the enzymes known to exist in the developing, and possibly even in the ageing, placenta likewise produce a lowering of the antithrombin content of the serum of both mother and child during pregnancy. The effect on the level in the blood of both foetus and mother and the cessation of the influence in both shortly after parturition seem to point to the cause lying in the placenta. The absence of any concrete evidence in support of this theory does not, however, influence the use of the test as an empirical aid to the diagnosis of pregnancy.

Summary

In 120 cases of pregnancy, varying from four weeks' duration to full term, the serum antithrombin level in every case has been found to be much lower than that of normal serum. The examination of 41 sera obtained post partum shows that the titre remains low for at least four weeks but returns to normal some time between five and twelve weeks after delivery.

It is suggested that the test may be useful as aid to the diagnosis of pregnancy in certain obstetric problems.

We are indebted to Dr. J. Murray, Director of the Pathology Department of Queen Charlotte's Maternity Hospital, London, for supplying the sera from pregnant and post-partum women and for the cord bloods; to Dr. C. Upjohn, of St. Helier Hospital, Carshalton, for supplying the sera from the newborn; and to Mr. G. W. Cecil, for much expert technical assistance.

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"Every scholarly discipline breeds its own jargon . . . jargon is a legitimate form of short-hand conveying in a phrase several related ideas, but too often a deep-seated mental laziness pervades the scholar who uses it as *cliché*. He also uses it as a drug to deaden his fears. He longs for anonymity, an anonymity which protects him from the biting attacks of other scholars. If he can reduce his own personality to the smallest proportions by employing such terms as 'the present writer,' by using verbs in the passive rather than the active tense and by eliminating every sign of an individual having written the work, he hopes his critics will not notice that he has written it" (*The Times Literary Supplement*, July 16, p. 458).

METHAEMOGLOBINAEMIA DUE TO NITRATES AND NITRITES IN DRINKING-WATER

BY

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Methaemoglobin may be present to a small extent in the blood of normal persons, the actual range found depending to some extent on the method of estimation employed. Bodansky and Bodansky (1952) quoted values ranging from 0.6 to 1.8% of the total haemoglobin (average 1.28%), using a gasometric method, while the more usual spectrophotometric method, after conversion by NaCN to cyanmethaemoglobin, gave the much lower range of 0 to 1.1% (average 0.4%). The level at which cyanosis becomes apparent will depend on the haemoglobin concentration of the patient, being obviously more apt to occur if the total available haemoglobin is low. The condition is exacerbated by anything which increases oxygen consumption, such as heavy exercise or pyrexia.

Apart from the congenital condition of familial idiopathic methaemoglobinaemia, described by Breakey *et al.* (1951) and Codounis (1952), in which cyanosis is usually present from birth, methaemoglobinaemia may be acquired by the ingestion of a number of substances, both organic and inorganic. Nitrites in drinking-water are a possible source which may be easily overlooked. Nitrates can also cause the condition by being converted to nitrites by intestinal bacteria. Campbell (1952) reported from Northern Ireland a case of cyanosis in a 1-month-old infant due to nitrates in the water used to make up its feeds. Recognition in infants of cyanosis due to methaemoglobin formation is important, as the case may be initially mistaken for one of congenital heart disease.

A similar case recently occurred locally in a 5-weeks-old girl, also due to nitrates (and some nitrites) in the well-water used for making up feeds. It would seem that a pyrexia initiated the attack of cyanosis in this case. A further point of interest is that the mother and two elder children, who had all been drinking the same water for over a year, suffered no ill effects as a consequence, although they all showed significant amounts of methaemoglobin in their blood. The case reported by Campbell responded well to large doses of ascorbic acid, and the same treatment was applied here with satisfactory results.

Case History

The patient, an infant girl aged 5 weeks, was the youngest of a family of three children (the other two children were both well). Her birth weight was 6¼ lb. (2.8 kg.). The delivery was normal. The child was said to have been slightly cyanosed at birth and jaundiced from the third to the tenth day. Progress was otherwise satisfactory. She was breast-fed for the first month, and then, as breast milk failed, placed on a four-hourly feed of 3 oz. (85 g.) of full-cream national dried milk, with 1½ dr. (6 g.) of sugar in 3½ oz. (100 ml.) of water. Owing to the housing shortage the family were obliged to live in a caravan, and the water was obtained from a near-by well. She had been on this artificial feed for approximately one week prior to admission. Three days before admission she became pale and feverish, and then cyanosed. She was admitted to hospital on July 22, 1953.

On examination her general development was fair. She was severely cyanosed and crying. Her temperature was 102° F. (38.9° C.), pulse 148, and respirations 50. The heart sounds were normal; no murmurs. There was nothing abnormal in the chest, abdomen, mouth, throat, and ears. Blood: haemoglobin, 93%; white cells, 16,600 per c.mm. (54% polymorphs). In view of the cyanosis the child was placed in an oxygen tent, but without improvement. She also received penicillin, 125,000 units six-hourly. *X*-ray examination of the heart and lungs showed no physical abnormalities, which, together with the absence of physical signs, made it necessary to look for some cause of the cyanosis other than a cardiac or respiratory lesion. Initial spectroscopic examination of the blood revealed the presence of methaemoglobin. Photometric estimation showed the amount to be 56.8% of the total pigment.

The child was put on ascorbic acid, 1,000 mg. daily by mouth for three days. Within 48 hours the cyanosis had completely disappeared, her temperature had returned to normal, and she was taking her feeds quite well. Repeated blood examination three days later showed no methaemoglobin present.

While the child was in hospital, the possible cause of the methaemoglobinaemia was investigated. Poisoning by drugs, etc., likely to cause methaemoglobin formation and ingestion of aniline dyes—for example, by absorption from napkins—both seemed very improbable after questioning the mother. A sample of well-water used for making up the feeds was collected and analysed. The result showed the presence of excessive nitrate and some preformed nitrite (Table I).

TABLE I.—*Analysis of the Well-waters (Parts per* 100,000)

	Caravan Well		Inn Well
	10/7/53	10/12/53	
Free and saline ammonia ..	0·01	0·043	0·003
Albuminoid ammonia	0·005	0·01	0·01
Nitric nitrogen (nitrates) ..	7·8	7·2	3·5
Nitrous „ (nitrites) ..	0·02	0·08	Trace
Oxygen absorption test	0·17	0·33	0·07
Toxic metals	None detected		

The infant was discharged a week later, July 10. The mother was advised to find an alternative supply of water and report back with her on July 28. Unfortunately the next supply of water was drawn from a near-by inn, which also used a well. This water, although rather better than the previous well-water, had considerable excess of nitrate and traces of nitrite (Table I).

On July 24 the mother reported the child to be cyanosed again. This time, however, cyanosis was less marked, and occurred chiefly in the evenings. It was not feasible to re-examine the child's blood for methaemoglobin, but as the cause was now known the mother was given a supply of ascorbic acid, the dosage to be 500 mg. for two days and then 100 mg. for one week. She was advised to get water from the city mains supply for making the feeds. The father collected this each evening on his way back from work, and continued to do so. Progress continued as follows:—August 4: no more cyanosis since the introduction of town water; ascorbic acid discontinued; weight 8 lb. 9 oz. (3.9 kg.). September 8: child well; no further cyanosis; weight 10 lb. (4.5 kg.). November 6: child well; weight 11 lb. 14 oz. (5.4 kg.). December 8: satisfactory progress maintained.

On December 8 the child's blood was re-examined for methaemoglobin, which was found to be absent. Since the remainder of the family were still using the well-water and seemed likely to have to continue doing so for some while, the whole family was examined (Table II), although none of them had complained of any ill effects.

Methaemoglobin was determined by the photometric method of Evelyn and Malloy (1938). The method as

TABLE II.—*Methaemoglobin Formation from Nitrates and Nitrites in Water*

Date	Subject	Total Hb % of Normal (Haden) (100%= 15·6 g./100 ml.)	Methaemoglobin as % of Total Hb	Drinking-water Supply
4/7/53	Baby (cyanosed)	93	56·8	Well
8/12/53	„ (cured)	80	Nil	Town
„	Child (aged 2)	75	16·7	Well
„	„ („ 3)	70	9·5	„
„	Mother	77	9·5	„
11/12/53	Father	90	Nil	Well-water at night; meals out during the day

described is applicable to the Evelyn–Rubicon photometer, whereas the instrument used here is similar to that described by Salt (1950), fitted with a Tinsley galvanometer. An instrument-correction factor was therefore worked out by means of known solutions of methaemoglobin, and has been applied to the values quoted.

Comment

It can be seen that those members of the family whose water supply was derived entirely from the well all showed levels of methaemoglobin far above the upper limit of the normal range for this method of estimation. The baby, who had been receiving town water for a matter of four months, and the father, who fed out at canteens during the day, both gave negative results.

This short study emphasizes that where a family are relying on a water supply of high nitrate or nitrite content a young baby is more prone to show the effects of methaemoglobinaemia than its elders, as its daily intake of the water, on a weight-for-weight basis, is much larger. Symptoms may be precipitated by the onset of a pyrexial illness, increasing its oxygen demand. Also, if a baby from a rural area presents with a cyanosis unexplained by physical examination, investigations of the water supply may prove to be time well spent.

We are grateful to Mr. M. M. Love, county analyst, for kindly carrying out the water analyses for us.

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Changes in the law governing the production and supply of milk in Scotland come into force on October 1. The changes represent further steps towards securing a safe and clean milk supply. Bottles of pasteurized milk will have to be fitted with caps which seal the lip of the bottle, and bottling will have to be done on the premises where pasteurizing takes place. This is to prevent milk being handled after it has been pasteurized. The special designation "standard" will not be recognized after September 30. In "specified areas," which include all cities and large burghs and many small burghs and landward areas, the sale by retail of standard milk will be forbidden. The only grades of milk allowed to be sold in these areas will be certified, tuberculin tested, pasteurized, and sterilized. A producer's licence to use the special designations certified or tuberculin tested will be granted from October 1 only if the herd from which the milk comes is attested or is in a tuberculosis eradication area of the Ministry of Agriculture and Fisheries. The effect of this is that certified and tuberculin tested milk will in future come from farms where all the cattle, and not only the milk cattle, are certified to be free from bovine tuberculosis.

STAPHYLOCOCCAL FOOD-POISONING DUE TO INFECTED COW'S MILK

BY

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AND

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Although *Staph. pyogenes* is commonly found in cow's milk, outbreaks of food-poisoning arising from such a source are relatively very rare. This fact also makes a definite diagnosis difficult, since the isolation of these bacteria from milk or milk products during the investigation of an outbreak of food-poisoning does not imply that they are the cause of it.

This account of two small related outbreaks of food-poisoning is not without interest in that the infective agent, clotted cream, was prepared from milk from a cow that was found to be persistently excreting *Staph. pyogenes* in her milk. Furthermore, the staphylococcus was of a type rarely found in bovine infection, that type being predominantly a human pathogen.

The Outbreaks

On January 9, 1954, notification was received that a small outbreak of food-poisoning had occurred on the previous evening. Seven persons in one family were involved (Table I), and the suspected food was home-made clotted cream. The cream was eaten at 4.30 p.m. and was followed in six cases, in three to three and a half hours, by the abrupt onset of nausea, abdominal pain, and vomiting followed by diarrhoea. In the seventh case symptoms were confined to nausea and general malaise. No case required admission to hospital, but all except the seventh patient were incapacitated for a period varying from six to forty-eight hours.

TABLE I.—*Persons Involved in Outbreak on January 8, 1954*

	Age	Onset	Duration	Nausea	Vomiting	Diarrhoea
Mr. S. ..	67 ?	4 hours	3 hours	+	−	−
Mrs. S. ..	48	3 „	6 „	+	+	+
Mrs. B. ..	45	3–3½ „	48 „	+	+	+
John B. ..	12	3½ „	12 „	+	+	+
Mrs. G. ..	73	3½ „	24 „	+	+	+
Miss H. ..	74	3½ „	24 „	+	+	+
Miss C. ..	66	3½ „	20 „	+	+	+

Further investigations revealed that clotted cream prepared from the milk of the same cow was eaten without ill effect on December 26 but that a similar incident had occurred on January 2 following consumption of the cream by another family living on the same premises (Table II). The cream was prepared on all occasions in a similar manner, on January 2 by Mrs. S. and on January 8 by Mr. S.

TABLE II.—*Persons Involved in Outbreak on January 2, 1954*

	Age	Onset	Duration	Nausea	Vomiting	Diarrhoea
Mr. W. ..	55	3 hours	30 hours	+	+	+
Mrs. W. ..	57	2 „	30 „	+	+	+
Mrs. H. ..	59	3 „	30 „	+	+	+
Mr. A.* ..	21	—	—	−	−	−

* Mr. A. ate only a very small amount of cream, "Less than a teaspoonful."

The cow, a single-house cow, was always milked by Mr. W. It had calved on December 12, 1953, and had not shown any signs of mastitis. Clinical examination revealed the udder to be normal, and the milk from each quarter

was quite unchanged, macroscopically or microscopically. The milking routine was satisfactory, and examination of food-handlers revealed nothing of any significance—for example, head colds, small septic-finger lesions, etc.

Bacteriological Examination

A specimen of the clotted cream received on January 9 yielded a profuse growth of *Staph. pyogenes* on blood agar. This organism was also isolated from a composite milk sample taken with sterile precautions from the four quarters of the cow's udder.

On January 19 nasal and throat swabs from Mr. and Mrs. S. and Mr. W., and milk samples from each quarter of the cow were examined. Large numbers of *Staph. pyogenes* were present in the left nostril of Mr. W. and smaller numbers in the left fore-quarter of the cow. Staphylococci were not grown from any of the other specimens. On January 29 the above examination was repeated with similar results. On this occasion a swab was also taken from the back of Mr. W.'s right hand; *Staph. pyogenes* was recovered from it on culture.

The cultures referred to above showed the characteristics usually associated with *Staph. pyogenes*, but two of their properties merit special reference. Firstly, when tested for haemolysin production by the method of Elek and Levy (1950) they were all found to produce α and δ toxin but no β toxin. Secondly, they produced opacity in egg yolk when tested by the method of Gillespie and Adler (1952). They were phage-typed by Dr. R. E. O. Williams, of the Staphylococcal Reference Laboratory, Colindale, who reported that they all had the same phage pattern, 53+.

On January 29 clotted cream was made by exactly the same methods that had been used on previous occasions, bacterial counts being carried out at appropriate intervals by the method of Miles and Misra (1938). The results are shown in Table III. No other bacteria were found to be

TABLE III

Time and Technique	*Staph. pyogenes* × 10^4 per ml.	
	Cream	Milk
January 29, 8 a.m. Cow milked; milk then placed in china jug in pantry and left for cream to rise.		
9 a.m.	—	1·25
January 30, 10 a.m.	2·5	0·02
Jug placed on plate of Aga range.		
6 p.m.	2,000	50
Left in pantry overnight.		
January 31, 10 a.m.	7,500	45

present. No detailed temperature recordings were made while the cream was on the range, although a temperature of 38° C. was recorded on one occasion.

Discussion

The available evidence indicates that *Staph. pyogenes* was responsible for the outbreak of food-poisoning. The origin of the strain of that organism is of some interest. Dr. R. E. O. Williams reported that strains of *Staph. pyogenes* having a phage pattern identical with or closely similar to our strain of *Staph. pyogenes* are fairly commonly isolated from human beings and have been incriminated in outbreaks of food-poisoning. He points out, however, that this type of staphylococcus has been isolated from materials from cows. Macdonald (1946) and Smith (1948) found that most staphylococci isolated from milk belonged to phage-type 42D. Phage 53 was not in use when they carried out their work, but since the number of untypable strains they encountered was small it can be concluded that phage-type 53 is, at least, not commonly found in milk. A consideration of the other properties of our strain is probably of greater interest, as it did not produce β toxin, a toxin which is characteristic of strains isolated from cattle—for example, Minett (1936), Smith (1947), and Elek and Levy (1950). Again, it is noted that our strain produced opacity in egg yolk. Adler, Gillespie, and Herdan (1953) found that 84.1% of strains of human origin but only 12.9% of strains isolated from cow's milk or from cases of bovine mastitis possessed this property. It is therefore probable that the strain of *Staph. pyogenes* responsible for this outbreak of food-poisoning was of a type that is usually associated with human beings and that the origin of the infection in the cow's quarter was a focus in the nose of Mr. W., the milker. If this was the case it is noteworthy that it did not prevent Mr. W. becoming a victim of the food-poisoning.

In the absence of any detailed information about the character of staphylococci isolated from milk or milk products that have been incriminated in outbreaks of food-poisoning it is tempting to speculate why so few outbreaks have been caused by the consumption of these foods despite the fact that they often contain *Staph. pyogenes*. One explanation that received support from the observations made during the investigation of the present outbreak is that the staphylococci that usually infect the cow's udder do not produce enterotoxin. It is realized that other explanations are also quite possible.

Summary

Two small outbreaks of staphylococcal food-poisoning caused by clotted cream prepared on two different occasions from the milk of the same cow are described.

Staph. pyogenes was found to be present in the milk from one of the quarters of the cow's udder on several occasions. The same type of staphylococcus was also isolated from the nose of the milker. The characters of these strains of staphylococci more closely resembled strains of human than bovine origin.

ADDENDUM

After these two outbreaks of staphylococcal food-poisoning steps were taken to deal with the two staphylococcal carriers—Mr. W., who was responsible for the milking, and the cow concerned.

In the case of Mr. W. the condition apparently cleared up after treatment with sulphonamide and penicillin, negative nasopharyngeal swabs being obtained. Negative bacteriological results were also obtained from culture of samples of milk from the cow on two occasions, following treatment with repeated intramammary injections of procaine penicillin cereate.

The household then recommenced to drink milk and cream in its raw state and with no ill effects until May 14—which happened to be a freak weather period with maximum day temperatures approaching 80° F. (28.7° C.). On this occasion skimmed cream was the offending vehicle of infection, and was eaten by Mr. W., Mrs. W., Mrs. B., and Miss H., only a very small quantity being eaten by Mr. W., who was unaffected; but the three latter were taken acutely ill with nausea, diarrhoea, and vomiting about three hours later.

Specimens were taken for bacteriological examination as follows: (1) Samples of cream remaining from the meal were found to contain approximately 10^7 viable staphylococci (type 53+) per ml. (2) A sample of milk from the same quarter as was affected in the earlier outbreak was found once more to be excreting 10^3 staphylococci (type 53+) per ml. (3) A nasal swab from Mr. W. gave a profuse growth of staphylococci (type 53+). (4) Staphylococci (type 53+) were cultured from faeces of Mr. and Mrs. W. On this occasion faeces were also examined for organisms of the salmonellae–shigellae group by culture on desoxycholate–citrate–agar medium with and without previous enrichment in selenite-f, with completely negative results.

The cream was prepared by skimming milk which had been allowed to stand overnight in a pantry from milking-time, 4 p.m., on the previous day. The cream thus obtained was placed in a refrigerator from 10 a.m. until eaten at 7 p.m.

This last outbreak in this series of three related outbreaks is noteworthy in that it is a clear demonstration that a recent attack of staphylococcal food-poisoning confers no immunity.

We are grateful to Dr. R. E. O. Williams for help and advice.

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Medical Memoranda

Smoking and Lung Cancer

For purposes of comment the results recorded by Dr. R. Doll and Professor Bradford Hill in Table III on page 1273 of the *British Medical Journal* for December 13, 1952, have been graphed. The degree of cigarette-smoking is specified by them in the following way: 1 Cig.–, 5 Cigs.–, 15 Cigs.–, and so on. It is perhaps least open to objection to plot, for any particular range, the average value, and this has been done in the graphs of Fig. 1. We are not entitled

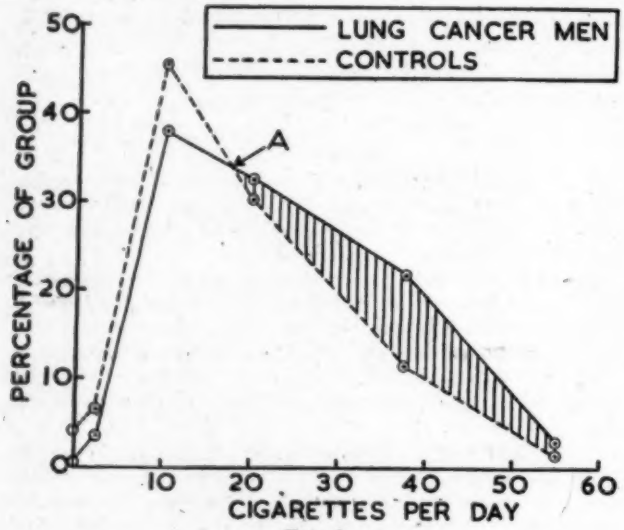

FIG. 1

to conclude from this that heavy cigarette-smoking is the cause of lung cancer; a strictly impartial comment would be that "it will be seen that there is a higher percentage of heavy smokers among the cancer men than among their controls."

Cause and effect are not always easily distinguishable. If an inquiry showed that men with cancer of the stomach took more alcohol than their controls it would be quite rational to look upon a little excess of alcohol as the effect and not the cause of the disease; it might be like this with smoking.

The two graphs intersect at the point A; here we find the two groups of men smoking cigarettes to the same degree. Is one entitled to conclude that those who have lung cancer contracted it *because* of their cigarette-smoking? It has to be remembered that for every lung-cancer man we are thinking of in connexion with smoking there is not only his opposite number serving as control in the statistical investigation by Doll and Hill, but there is quite a large number. At this stage it is convenient to bear in mind a useful quantity—namely, the number of men who have lung cancer at the present time.

The senior economist in the U.S. Public Health Service investigated the relation between the number of people ill from cancer and those dying from the disease in that country. From the information he obtained he was able to derive a ratio which, multiplied by the number of cancer deaths per year, gives approximately the number of people suffering from cancer at any moment within the period examined. Assuming that survival with cancer does not differ much in the two countries, and applying this same multiplying factor to our own present yearly total of deaths —for example, 75,000 in 1950—we derive the approximate figure of 150,000; the factor for all forms of cancer being about two. In the case of lung cancer the factor is almost certain to be less than two because the clinical course of the disease is shorter than the average for cancer; with a yearly mortality for cancer of the lung of 15,000 (10% being women) we shall be erring on the right side by putting the number of lung-cancer men at this moment as 30,000. There are about 12,000,000 men in England and Wales between the ages of 25 and 75, but their age distribution is not the same as that of lung-cancer men. Consequently we cannot say that there are available 400 controls to every cancer patient. If we halve this number and say 200, we shall probably be making a safe allowance for this difference in age distribution. Hence for any lung-cancer man in the Doll and Hill series there will be one man chosen as control out of an average of about 200; it will not always be 200, as we shall see.

If as an example we select the 10-cigarettes-per-day man, for every lung-cancer man there are about 200 similar smokers without cancer. Are we to conclude that if the one man in several hundred who gets lung cancer smokes 10 cigarettes a day as do the others, then smoking has caused the lung cancer? It is possibly true, but is not the long arm of causation being unduly stretched in maintaining the same position for all and every grade of cigarette-smoking?

Dr. Doll writes in the *British Journal of Cancer* of September, 1953: "Even very heavy smoking does not appear to be uniformly carcinogenic."

A man who smokes 40 cigarettes a day can perhaps be reckoned a very heavy smoker. A glance at Fig. 1 shows that of the group there were 19% lung-cancer men and 10% controls in this category, say 2:1. To get a proper perspective in this matter it must be remembered that the control non-cancer man is one out of *about* 100 who could serve as controls; so that it is one very heavy smoker who gets lung cancer as against 100 similar smokers who do not. Dr. Doll may be said to be indulging in a somewhat inverted meiosis in his statement.

In view of the fact that smoking is a widespread habit it would be of the greatest interest to compare the death rates from lung cancer in different countries with their smoking experiences. Unfortunately, there are very few countries which have the requisite data in appropriate form for any such comparison. With what data were available, however, Dr. Doll has drawn a graph in which death rates from lung cancer are plotted against the degree of cigarette-smoking. I have reproduced this as faithfully as I can in Fig. 2. Dr. Doll writes: "I doubt whether much significance should be attached to the result, *but it is not inconsistent with the existence of a relationship between lung cancer and cigarette-smoking.*" The italics are mine.

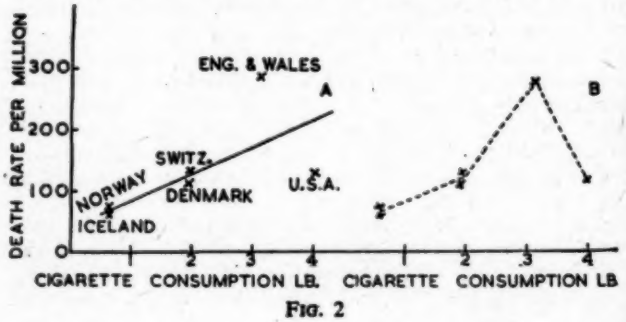

FIG. 2

To the reader it might appear that Dr. Doll was intent on seeing that a straight line should go through the datal points; but if we proceed on the usual lines by joining up points in sequence we get the graph to the right of Fig. 2, from which it will be seen that there is no simple relation between the death rate from lung cancer and the degree of cigarette-smoking. The people of the U.S.A. are the largest per person cigarette-smoking people in the world, yet their lung-cancer death rate is about the same as that of the people of Switzerland and Denmark, who smoke about one-half of the cigarette quota of Americans. It is to be accepted as a fact that people in England and Wales with lung cancer do on the whole smoke more cigarettes than control people of the same age group, but the fact that as we go from one country to another no relationship exists between cancer death rates and the degree of cigarette-smoking seems to point to something quite significant; surely there must be some other factor or factors at work. This is not a matter of academic interest but one of high practical importance. If cigarette-smoking is responsible for the majority of deaths from lung cancer, how is it that people in the U.S.A., who smoke about 30% more cigarettes than we do, show a death rate from lung cancer (1950) less than half that of ours? The respective rates are 120 and 280 per million inhabitants.

Whether smoking is, or is not, one of the causes of lung cancer in our midst, there will be few people to dissent from the warning given by the Minister of Health (February, 1954) to young people on the dangers of excessive smoking. All excess is bad.

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Fatal Case of Toxic Hepatitis Implicating Chlorpromazine

Chlorpromazine has been used on 500 psychiatric cases (to be reported subsequently), of which six developed jaundice. The one ending fatally is here described.

The issue is clouded by the fact that three cases diagnosed as infective hepatitis have occurred concurrently in patients who had never received chlorpromazine or other liver toxin. These cases have been clinically and biochemically indistinguishable from the chlorpromazine cases. The incidence of jaundice in the latter, however, is significantly higher than among the rest of the hospital population.

CASE REPORT

The patient, a woman aged 45, with a recent history, was admitted in a severely disturbed, excited, restless, overactive state with a paranoid psychosis. She showed a mitral stenosis, normally asymptomatic, which at her current level of activity led to dyspnoea and cyanosis. Her blood pressure was 130/80. As sedation was not consistently successful, she was given oral chlorpromazine, the dosage being quickly stepped up to 500 mg. a day. Aided by amylobarbitone sodium in doses not exceeding 36 gr. (2.4 g.) a day, the excitement and overactivity abated, the mental content becoming progressively more rational and coherent. After three weeks of this regime, when 10 g. of chlorpromazine had been consumed, jaundice appeared, so the drug was withheld. A 24-hour pyrexia of 101° F. (38.3° C.) had preceded the jaundice by four days.

Throughout the ensuing 13 weeks the serum proteins, thymol turbidity, and colloidal gold were normal. Alkaline phosphatase remained between 20 and 30 Armstrong units, apart from a terminal climb to 70. Serum bilirubin rose to a peak of 23 mg. per 100 ml. by the end of the third week, thereupon declining to a level of 16–18 mg. per 100 ml. Throughout, the "direct" component of the serum bilirubin was two to two and a half times as great as the "indirect." Blood counts showed no significant change.

The liver was enlarged from the onset, but its margin rose and fell several times for no apparent reason. It was regular and never tender. Stools were pale or near-white; the urine was heavily laden with bilirubin. Her appetite was good until the last week. Itching was present during the earlier weeks. Prior to death in stupor, auricular fibrillation supervened.

Necropsy (Dr. David Haler) showed an enlarged nutmeg liver, double mitral and aortic lesions, purulent terminal pericarditis, and congestive heart failure. Microscopy of the liver supported a diagnosis of toxic hepatitis.

Comment.—It is now generally accepted that chlorpromazine is toxic to some apparently healthy livers, and even more so to those already diseased. It would appear from this case that passive congestion of the liver renders it vulnerable. No mechanism explaining this toxic effect can be offered, nor any prophylaxis suggested other than the orthodox dietary measures.

My thanks are due to Dr. H. C. Beccle, medical superintendent, to Dr. David Haler for conducting the necropsy and to Dr. R. Forgan, of May and Baker Ltd.

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Removal of Rubber Teat from Intestine of an 8-weeks-old Baby

A child born on October 20, 1952, by normal delivery, birth weight 7 lb. (3.2 kg.), was admitted to hospital at 11.30 a.m. on December 17. The history was that two days before admission it had started vomiting and had vomited every feed since then. It had been breast-fed for six weeks, and a week before admission had begun feeding on full-cream National dried milk, and had become constipated and then had diarrhoea; it then again became constipated for two days before admission. The vomit was projectile, consisted of milk, and usually occurred during the feed.

On examination the child looked marasmic and was in a very dirty condition. It was dehydrated and had depressed fontanelles of the skull. When fed on admission it had projectile vomiting, but there had been no visible peristalsis, and no tumour was felt. After every feed that was now given there was projectile vomiting, and the vomit contained bile. On December 23 the child was screened after a barium meal and was found to have an obstruction in the jejunum, 1–2 ft. (30–60 cm.) from the duodeno-jejunal flexure.

The patient was referred to me by the paediatrician for a surgical opinion, with a diagnosis of intussusception. On examination there seemed to be a mass in the left hypochondrium which came up to meet the palpating fingers but which disappeared on deep palpation.

Operation was carried out on December 23 through a right paramedian incision. A distended loop of small gut presented in the wound. On palpation the obstruction was found to be due to a rubber teat in the jejunum, about 2 ft. (60 cm.) from the duodeno-jejunal flexure. A longitudinal incision was made over the jejunum and the teat removed. The bowel was sewn up transversely with interrupted silk sutures, and the wound closed in layers. The child made an uninterrupted recovery and was discharged from hospital on January 12, 1953.

The only reference which I could find to a previous case was a case of Lawson's (1899) in which a 6-months-old baby was playing with a "comforter," and the parents knew that the baby must have swallowed it. On this occasion the patient was treated by observation, and four weeks and four days later the teat was found lodged in the baby's anus.

An interesting point is the fact that if, on examination of a case of intussusception, a mass is found on light palpation which disappears on deep palpation, it may be due to the presence of a teat in the small bowel as in the present case.

My thanks are due to Dr. J. G. Dathan for referring this case to me, and to Dr. C. Hayes for the anaesthesia.

G. GORDON CROWE, F.R.C.S.Ed.,
Consultant Surgeon, Stoke-on-Trent Hospitals.

REFERENCE

LAWSON, G. L. (1899). *Aust. med. Gaz.*, 18, 225.

Reviews

HIP ARTHROPLASTY

Resection-Reconstruction of the Hip—Arthroplasty with an Acrylic Prosthesis. By Jean Judet, Robert Judet, Jean Lagrange, Jean Dunoyer. Edited by K. I. Nissen. Original edition published in French by L'Expansion Scientifique Française. (Pp. 151; 101 figures. 30s.) London and Edinburgh: E. and S. Livingstone. 1954.

Jean and Robert Judet made an interim report on their experience of 400 operations of resection–reconstruction in 1952. By November, 1953, this experience was more than doubled. In this book and in all their writings they declare with modesty the necessity of drawing conclusions only after adequate clinical trial. The editor of the English volume has helped to produce a readable and very specialized monograph. The subject is narrow, but it is of great importance owing to the prevalence to-day of chronic arthritis. The book is no textbook, but is essentially practical and likely to be of help to those surgeons who contemplate a visit—or have already made one—to the clinic where the work is in progress.

The arrangement of the chapters is unorthodox in that the analysis of results and complications of resection–reconstruction form the subject-matter of the first two chapters. These practical surgeons give a full enough discussion of the conditions and types of joints which may be treated by this operation to make the reader realize that they have given thought to pathology as well as to mechanics. Hence chapters are found on osteoarthritis, fresh and ununited fractures of the neck of the femur, traumatic arthritis, sequelae of septic arthritis, and tuberculous arthritis.

The chapter on congenital dislocation in adults indicates that experience of its treatment by this method is small, as is also the treatment of fresh subcapital femoral fractures by resection–reconstruction. The operative technique is adequately described, and the reasons for using a certain shape and a particular plastic material for the prosthesis are explained. Post-operative care and rehabilitation are planned. End results, and interim results, are classified as good, fair, and poor, although the excellent classification according to pain, movement, and walking (or function) is appreciated early in the book.

The paper and print are of a high quality and the reproduction of radiographs excellent and of a useful size. Some small diagrams are most helpful. The various stages of the operation are shown in nearly thirty photographs. Although much trouble has been taken to represent detail, most of them are of little value and no substitute for a few hours in the Judet operating theatre. This volume is an asset to the libraries of English-speaking surgeons. The authors and editor have written with enthusiasm and yet moderation at a time when arthroplasty is again attracting attention.

ST. J. D. BUXTON.

THE KIDNEY

Ciba Foundation Symposium on the Kidney. Arranged jointly with the Renal Association. Editor for the Renal Association A. A. G. Lewis, B.Sc., M.D., M.R.C.P. Editor for the Ciba Foundation G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., assisted by Joan Etherington. (Pp. 333+xiii; 125 illustrations. 32s.) London: J. and A. Churchill Ltd. 1954.

This is an account of a symposium arranged jointly between the Ciba Foundation and the Renal Association. It is produced with the editorial care we have come to expect from the Ciba Foundation, and contains almost verbatim accounts of the discussions which took place after each paper. It is an exciting book, and conveys to the reader something of the enthusiasm and interest that marked the actual symposium of which it is a record. As it has been produced after not too long delay it can be considered a really up-to-date summary of the work at present going on in this subject—up to date, that is, to all except those who gave the papers, for they are no doubt already several moves ahead in their unpublished work.

One can only allude here to a few examples of the contents. In the section on structure, Jean Oliver and Darmady deal with tubular lesions and Flemming Raaschou with aspiration biopsy. Wirz, with an interesting paper followed by a lively discussion, describes and defends his ingenious theory of the formation of hypertonic urine in the loop of Henle. In the section on tubular function J. V. Taggart's communication on tubular transport mechanisms is perhaps the most exhilarating, for it discusses not merely what the tubule does but how it does it. On acid–base balance there are Pitts, Berliner, and others; and on other electrolyte problems Milne, Alwall, and Dent are among the speakers. The final section, with papers by Borst, Hamburger and Mathé, and Black, is on the renal share in volume control of body fluid; this is perhaps the most tentative, as it is bound to be at the present time.

This is a book which all those whose primary interest is in the kidney will want to read, and as a presentation of current thought on renal problems it should appeal to a much wider circle.

ROBERT PLATT.

ELECTROCARDIOGRAPHY

Electrocardiographie Clinique. By L. Lenègre, G. Carouso, and H. Chevalier. Preface by Professor Charles Laubry. (Pp. 810; 341 figures. 6,800 francs.) Paris: Masson et Cie. 1953.

This book is an important exposition of the most recent views held in France. The authors say they aim only at giving a medical man enough information to understand and read electrocardiograms correctly, but that is a very modest account of the vast field the book covers. There are several novel features in the presentation of the subject. We may remark at once on the excellent illustrations, which are quite faultless.

After a short chapter on the technique of electro-cardiography there is a short but clear account of the physiological aspects of the subject. This is well done and could easily be understood; once mastered, it forms the basis for all the rest. There is then a description of the normal electrocardiogram. The second chapter of this part adheres to the older approach through the standard leads; the unipolar praecordials come next and the unipolar limb leads last. The reviewer cannot help feeling that for the beginner it would be much easier if the last came first and the standard leads were emphasized less. For the experienced it does not matter. But this is the point of view throughout, and it seems a little old-fashioned. There is a useful chapter on the electrocardiogram in childhood. Then follows an excellent long analysis of the principal electrical syndromes, such as hypertrophy, coronary insufficiency, and bundle branch block. This forms the main part of the work. The theoretical part of the topic is first discussed and then there are illustrative cases. Well documented with operation or necropsy confirmation, it is here that the curves are shown. This is a very good idea, for it all serves to integrate the cardiographic findings with the rest of the clinical picture, and so brings them into their proper place. The next large chapter concerns the features of the electrocardiogram in the various states which cause disease of the heart. This part rather tends to repeat much of what was dealt with before, but it may be of advantage to have a different approach. The disorders of rhythm come last; here the theory of circus movement still survives intact. There are many references. The index is good. This is an interesting and stimulating work which brings modern electrocardiography well into the field of clinical cardiology; the expression throughout is a model of clarity and economy.

TERENCE EAST.

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CHLORPROMAZINE

For some time French workers have been testing the physiological, pharmacological, and clinical effects of various derivatives of phenothiazine. Most of these compounds have well-marked antihistaminic effects, and one of them, promethazine ("phenergan") is often administered. The latest addition to their number, chlorpromazine ("largactil"), has proved to have remarkably interesting properties. It has only moderate antihistaminic qualities, but appears to act as a depressant of neuronic activity at the cortical and hypothalamic levels and probably also more peripherally, since it potentiates the action of curare and curare-like drugs. Work done in the laboratory[1] has been confirmed clinically[2] and in the operating theatre.[3] It enhances the action of most narcotics, such as the barbiturates, ether, and ethyl alcohol, and in anaesthesia permits the dosage of these drugs to be reduced. Acting by itself it produces apathy and emotional indifference, and reduces emotional tension and the agitation or overactivity which may arise from it. The effects described in 1952 by Delay and Deniker[4] have since been to a considerable extent confirmed. An excellent general account has been given by Lehmann and Hanrahan,[5] though they particularly concerned themselves with the use of the drug in states of excitement. It has been used to produce states of "artificial hibernation" or continuous narcosis in which there is some drowsiness but not as a rule actual sleep.

The drug seems to be relatively non-toxic. Given over a prolonged period, the optimal dose may be between 30 and 300 mg. a day, and side-effects are rarely serious. Lehmann and Hanrahan record using up to 800 mg. a day. By far the most serious danger is damage to the liver. If big doses are to be used, a liver function test should be made beforehand and the urine tested for bile while treatment goes on. Many observers have reported jaundice—Dr. W. M. Chesney records two probable cases at p. 591 of the *Journal* this week—and at p. 579 Dr. R. H. Boardman records a death from hepatitis probably caused by chlorpromazine. The patient had passive congestion of the liver from cardiac valvular lesions, and it is of interest that the only other death so far reported was a case of delirium tremens in which there was cirrhosis of the liver.

When given intravenously or intramuscularly, chlorpromazine tends to cause a fall of blood pressure; at the beginning of treatment, before the individual reaction is known, patients should be kept lying down for half an hour after the injection. Shock or collapse is very rare. At the beginning of a course most patients feel drowsy after a dose, so that at first ambulatory patients are best given the drug at bedtime. Dryness or a nasty taste in the mouth, constipation, frequency or oliguria, palpitations, ataxia, skin reactions, and pyrexia have been observed with varying frequency, but have rarely been severe enough to forbid the use of the drug. The risks of long administration are not known; it is seldom given for more than a few weeks. Therapeutic effects seem to diminish, so it is possible that the drug might cause addiction.

Apart from its use in anaesthesia, chlorpromazine may prove to be a valuable aid in the treatment of conditions causing either bodily or mental pain and distress. Sadove and others[6] have found it useful in patients suffering from pain arising from malignant lesions. Analgesics previously found to be ineffective became effective when chlorpromazine was added to them, and the doses of effective analgesics could be substantially reduced. Many of these patients also suffered from nausea and vomiting, for which chlorpromazine was particularly beneficial. Most workers have found that with it patients put on weight.

It is possible that chlorpromazine may have an important field of application in psychiatry, as has been suggested by the French pioneers. Winkelman[7] has tried it out on a great variety of patients, including those suffering from psychoneuroses, affective psychoses, schizophrenia, and senile dementia. The report is an enthusiastic one, and the impression is gained that all classes of patients benefited, becoming less depressed and difficult. Lehmann and Hanrahan, using much larger doses than the French workers, found it of special value in manic-depressive psychoses when the patient was in a manic or hypomanic state, but also very useful in all states of excitement, including catatonic excitements, epileptic clouding of consciousness, and toxic confusional states.

Reports published in this *Journal* are more cautious. The well-designed experiment by Elkes and Elkes, described this week at p. 560, in which every patient was made to serve as his own control, provides definite evidence that the drug is of benefit.

[1] Courvoisier, S., *et al.*, *Arch. int. Pharmacodyn.*, 1953, **92**, 305.
[2] Laborit, H., *et al.*, *Anesth. et Analg.*, 1952, **9**, 232.
[3] Forster, S., *et al.*, ibid., 1952, **9**, 250.
[4] Congrès des psychiatres de langue française, Luxembourg, July, 1952.
[5] *Arch. Neurol. Psychiat. (Chicago)*, 1954, **71**, 227.
[6] *J. Amer. med. Ass.*, 1954, **155**, 626.
[7] Ibid., 1954, **155**, 18.
[8] *British Medical Journal*, 1954, **2**, 439.

Of the twenty-seven agitated chronic psychotics, one-quarter showed marked and two-thirds some improvement. These authors note that fundamental psychotic symptoms were not changed in quality, and regard the treatment as having a purely symptomatic effect on the intensity of affect. Even then, in their opinion, the results were not dramatic. The report of Garmany, May, and Folkson, which appeared in the *Journal* two weeks ago,[8] will be of assistance in deciding on the indications of treatment. With any new therapeutic method which appears in psychiatry, the tendency always is to try it out indiscriminately, and the effort to distinguish between classes of patients is too seldom seriously engaged on. Dr. Garmany and his colleagues have drawn distinctions both between diagnostic groups and between symptoms, and reach the conclusion that tension is the symptom *par excellence* which is favourably affected. Phobic and obsessional symptoms, depression, and hysteria were little benefited. Having no cases of acute and grave excitement, they were unable to confirm the very promising results claimed in that field. The results of the experimental study by Drs. N. P. Lancaster and D. H. Jones, reported at p. 565 of the *Journal*, tend to support this conclusion. Some of the physiological changes which go with states of increased emotional tension, but which were here caused by insulin hypoglycaemia, were significantly reduced in severity or incidence.

The suggestion arises, from this effect on tension, that the applications of chlorpromazine and of prefrontal leucotomy may overlap symptomatically. When states of tension can be expected to be of relatively short duration chlorpromazine may well be tried; and, if it is found to be temporarily helpful in long-standing and intractable cases, that might by itself provide some indication that the more radical surgical measure would be promising.

DETECTING LUNG CANCER

The only available therapeutic measure which holds out any prospect of cure for primary carcinoma of the lung is radical surgical resection, and the results of this operation remain somewhat disappointing even in the hands of our most experienced thoracic surgeons. Sir Clement Price Thomas (personal communication) has carried out this operation and has records of the outcome in 133 cases of primary lung cancer. Of these, 33 were resectable but not strictly operable, and only two in this group survived the operation for five years. The five-years survival rate for the whole series, including these advanced cases, was 25.5%, a figure which shows a significant improvement on results previously published but makes it abundantly clear that every available method which might help us to make earlier diagnoses must be vigorously explored. It is here that we encounter our major problem. No matter what diagnostic measure is used, we are dealing with a highly malignant growth which more often than not remains clinically silent during most or all of the period when its surgical treatment is most likely to be successful, and it is a tragic fact that a high proportion of clinically evident growths are surgically inoperable.

It is possible that patients in the early stages of the disease may consult their doctors in increasing numbers as middle-aged male tobacco addicts become more "cancer conscious," and general practitioners are now fully aware of the insidious nature of the disease in its operable stages. A reliable diagnosis can be made by bronchoscopy and submitting a fragment to histological examination. The main fallacy in this method lies in the disappointing fact that 25–30% of all primary lung cancers lie at the periphery of the organ. In addition to this there is the inevitable hazard associated with the removal of a histologically suitable fragment. In any case the operation of bronchoscopy with biopsy is a rather formidable business for the patient; it needs some fairly clear indication before it is undertaken, and it is clearly not a suitable procedure for investigating the larger number of suspected cases which are likely to appear if the section of the population at risk becomes more anxious about lung cancer than it now is. Radiological examination of the lung may provide a picture that is highly suggestive of carcinoma, but bronchoscopy may fail to reveal any definite evidence of malignant disease.

There remains the examination of the sputum for exfoliated malignant cells. Fifteen years ago most British pathologists would have condemned this diagnostic manœuvre as unscientific. Since then the evidence in its favour has become overwhelming, and, within certain limitations, it can be regarded as an essential and reliable part of the investigation of all cases of suspected lung cancer. For obvious reasons it should precede bronchoscopy. It will undoubtedly lead to the identification of an appreciable number of peripheral growths in which subsequent bronchoscopy is almost certain to be negative. In addition to this, the sputum examination is not infrequently positive when the growth is small and has not yet produced the pathological changes responsible for radiological abnormalities.

A recent paper by Jennings and Shaw,[1] of the

[1] *Thorax*, 1953, **8**, 288.

London Chest Hospital, is worthy of serious consideration. They examined the sputum in 395 cases which were eventually proved by necropsy or otherwise to have bronchial cancers. In 240 (61%) a tentative diagnosis of carcinoma was confirmed. The authors insist that for an adequate investigation six morning specimens must be examined, and these must be taken before or at least ten days after bronchoscopy. Of their own cases, 109 were inadequately examined. Of the remaining 286 cases, six specimens were examined from each, and 83.9% of this group were identified as malignant. An interesting comparison in the series from the London Chest Hospital showed that when sputum examination was omitted, and the diagnostic measures limited to bronchoscopy, biopsy, and other means, the percentage of undiagnosed cases remained as high as 55.5. On the other hand, when sputum examination was employed in addition to the above measures the percentage of undiagnosed cases fell to 18.5—that is, from more than half to less than one-fifth. Malignant cells were found in the sputum in about two-thirds of those patients who had peripheral growths which were out of reach of the bronchoscope. There were six false positive reports (2.5%) in a series of 563 non-malignant cases, but in this connexion it should be noted that small primary growths in lungs removed at operation or necropsy may escape detection unless carefully searched for, and experienced observers can testify that the cells of such small growths may freely exfoliate and occur plentifully in the sputum.

Clearly, if sputum examination is to be performed successfully as a means of diagnosis, specimens of sputum in all reasonably suspicious cases of this disease should be examined by an experienced cytologist. It is doubtful if such facilities are generally available in Britain at present. The clinical pathologist to a hospital serving an industrial population of 350,000 was asked if he employed sputum examinations as a routine measure in lung cancer. He replied that in order to deal with the problem he would need the whole-time services of an experienced pathologist who had had an adequate cytological training, and skilled technical assistance. These minimal requirements were unobtainable and he was therefore unable to deal with the problem, although fully convinced of the diagnostic value of the examination.

Cytological knowledge can be gained only by experience. If cytology is to play its increasingly important part in clinical diagnosis, more leisure must be given to far more pathologists to acquire the necessary diagnostic skill.

AETIOLOGY OF PYLORIC STENOSIS

For many years infantile hypertrophic pyloric stenosis has been described in textbooks of medicine as a congenital malformation whose appearance was probably attributable to inheritance. The mode of inheritance suggested was a recessive gene.[1] But since the condition was reported to be more common in boys than in girls, and in first than in later born children, it was recognized that manifestation was related in some way to sex and birth order. Recent evidence has confirmed the association with sex and birth order, but has raised doubts both about the acceptability of the genetical hypothesis and whether the condition can any longer be regarded as a congenital malformation.

On this last point opinion has always been to some extent divided. Those who believed the abnormality was present at birth were impressed by its occasional appearance within a few days of birth, as well as by reports that it had been observed in stillbirths. The evidence on stillbirths is slender, however, and in spite of the large number of necropsies which have been performed appears to consist of no more than a single case. Moreover, direct evidence that the condition usually develops after birth was provided by Wallgren,[2] who found no abnormality at birth in radiographs of five infants who later developed the disease, and by McKeown, MacMahon, and Record,[3] who noted that the size of the pyloric tumour was sharply related to age at operation. There were no large tumours in patients submitted to operation within three weeks of birth (indeed, in several cases there was no tumour), and the proportion of large tumours increased regularly from the third week.

Investigations of inheritance have been handicapped by doubts about the diagnosis, and until recently observations on familial incidence were restricted mainly to brothers, sisters, and cousins of affected children. Incidence in brothers and sisters (about 10% and 2% respectively[1 4]) is nearly twenty times higher than in the general population of births, but incidence in cousins is apparently not raised.[4] It has also been reported that pyloric stenosis is uncommon among parents of patients, but the reliability of the history is open to question. Sufficient time has now passed, however, to make it profitable to consider

[1] Cockayne, E. A., and Penrose, L. S., *Ohio J. Sci.*, 1943, **43**, 1.
[2] *Amer. J. Dis. Child.*, 1946, **72**, 371.
[3] *Lancet*, 1951, **2**, 556.
[4] McKeown, T., *et al.*, *Ann. Eugen. (Camb.)*, 1951, **16**, 260.
[5] *Lancet*, 1954, **1**, 746.
[6] Lamy, M., *et al.*, *Proc. roy. Soc. Med.*, 1953, **46**, 1062.
[7] Powell, B. W., and Carter, C. O., *Arch. Dis. Childh.*, 1951, **28**, 45.
[8] Metrakos, J. D., ibid., 1953, **28**, 351.
[9] Ibid., 1952, **27**, 386.

offspring of the earliest patients whose diagnosis was well established, and Carter and Powell[5] have attempted to trace the 358 individuals who survived operations between the years 1920 and 1929 at the Hospital for Sick Children, Great Ormond Street, and St. Thomas's Hospital. In 85 cases they were successful; there were 46 children, of whom 3 had pyloric stenosis. An alternative estimate of incidence in children of patients was obtained by relating the number of known cases (7) in offspring of the 273 untraced men and women to the probable number of their children born since operation. In both cases the incidence is about the same as in sibs of affected individuals, and much higher than in the general population of births.

There is thus good evidence that the incidence of pyloric stenosis is raised substantially in children of affected parents, and in brothers and sisters of affected children. But the data cannot be fitted to any simple genetical hypothesis, unless we are prepared to make assumptions about the environment in which the gene is manifested, and to ignore the evidence that incidence in cousins of affected individuals is not raised. Indeed, the best reason for believing that genetical constitution is important in the aetiology is not the familial incidence, which could conceivably be explained by a common environment, but the higher incidence in males than in females, and the greater degree of concordance in identical than in fraternal twins.[6] That the environment also is important in the development of pyloric stenosis is suggested by the raised incidence in first-born children, and by the observation that only one of a pair of identical twins may be affected.[7 8] Until recently it was not clear whether the environmental influence is exerted before or after birth, but McKeown *et al.*[9] have recorded two observations which suggest that it is postnatal. They have shown that symptoms appear earlier in children born at home than in children born in hospital, and that in the first few weeks of life the disease is not associated with position in family. The last observation has been confirmed by Carter and Powell.[5]

On present evidence it seems probable that pyloric stenosis is not a congenital condition—that is to say, it is not present at birth. It is undoubtedly more likely to occur in some families than in others, but its familial incidence gives no support for any simple genetical hypothesis. Nevertheless there is no reason to doubt that inheritance is important in aetiology; there is also good evidence of the significance of the post-natal environment. It will be the task of future research to extend the familial studies and to attempt to define more precisely the nature of the environmental influence.

VIRAEMIA IN POLIOMYELITIS

The route by which virus reaches the central nervous system in poliomyelitis has long been studied. Earlier concepts of virus invasion in the human disease along the olfactory nerves or by lymphatic channels, based to a large extent on the findings of experimental poliomyelitis in monkeys, had to be discarded through lack of supporting evidence. Later opinion changed in favour of poliomyelitis as an infection primarily of the alimentary tract with secondary invasion along regional nerves, though clear-cut evidence in support of this neural route of invasion has never been produced.[1] Today this view is being seriously challenged in the light of recent advances in the pathogenesis of the disease.[2]

Experimental poliomyelitis in chimpanzees and cynomolgus monkeys after oral infection appears to be closely related to the natural human disease. In these primates viraemia regularly occurs in the incubation period[2 3] after the establishment of alimentary infection and before the onset of symptoms. Furthermore, antibody is invariably present at the onset of paralysis, and Bodian[2 4] has shown that passive immunization with comparatively small amounts of antibody will prevent paralysis but not the development of alimentary infection with active immunity. The significance of these findings is twofold. In the first place, the rate and amount of antibody development are very much greater than after intracerebral inoculation, suggesting an extraneural site of virus multiplication. Secondly, the presence of circulating antibody at the onset of symptomatic infection—and it is known that in man antibody is invariably present at the time a diagnosis is made[5]—might well affect attempts to recover virus from the blood at this stage of the disease.

Until recently, although numerous attempts had been made, virus had only been recovered from the blood of human beings on two occasions,[6 7] in one instance within a few hours of the onset of the minor illness. What was not clear at this time was whether the presence of virus in the blood was due to a spill-over from sites of active multiplication or whether it represented a definite stage in the disease process. Many years ago Draper[8] suggested that the failure to recover poliomyelitis virus from the blood or cerebrospinal fluid in human cases was due to the fact that none had been examined sufficiently early in their course. Two recent reports from the United States on the successful isolation of virus from the blood of contacts of cases of poliomyelitis support this view. During a poliomyelitis outbreak in Ohio in 1952 Horstmann and her colleagues[9] succeeded in recovering virus from the blood in 6 out of 33 patients infected with Type I virus. Virus was also recovered

[1] Bodian, D., and Howe, H. A., *J. exp. Med.*, 1947, **85**, 231.
[2] —— *Amer. J. Hyg.*, 1952, **55**, 414.
[3] Horstmann, D. M., *Proc. Soc. exp. Biol. (N.Y.)*, 1952, **79**, 417.
[4] *Amer. J. Hyg.*, 1953, **58**, 81.
[5] Hammon, W. McD., and Roberts, E. C., *Proc. Soc. exp. Biol. (N.Y.)*, 1948, **69**, 256.
[6] Ward, R., Horstmann, D. M., and Melnick, J. L., *J. clin. Invest.*, 1946, **25**, 284.
[7] Koprowski, H., Norton, T. W., and McDermott, W., *Publ. Hlth Rep. (Wash.)*, 1947, **62**, 1467.
[8] *Acute Poliomyelitis*, 1917, Philadelphia, p. 25.
[9] *J. exp. Med.*, 1954, **99**, 355.
[10] *Fed. Proc.*, 1953, **12**, 437.
[11] *J. exp. Med.*, 1951, **94**, 455.
[12] Ibid., 1953, **97**, 69; 455.

from the throat and rectal swabs. These were cases of asymptomatic infection and the minor illness only; one patient subsequently developed a non-paralytic form of the disease. Five of the patients had no antibody at the time virus was recovered, but in one patient who had antibody in low titre some difficulty was experienced in isolating the virus. Bodian and Paffenbarger[10] have also drawn attention to the early appearance of antibody in three cases of the minor illness in which viraemia had been established.

The concept of blood-stream spread as an essential phase of the disease is not universally accepted. Faber and his colleagues[11 12] are firm in their opinion that viraemia is secondary to a primary neurotropic infection. A closer and more extensive study of the human disease in all its stages, along the lines suggested by Horstmann and her colleagues, by improved laboratory methods, is indicated to decide the exact relationship of viraemia to invasion of the central nervous system.

GOUT

The end of meat rationing seems unlikely to make a great difference in the eating habits of the nation—or in the amount of gout. While in former days gross restriction of red meat and purine-containing substances was preached to, if not practised by, gouty patients, few physicians now have much faith in this measure. About half our excreted uric acid comes from endogenous sources and is not affected by purine intake. Marson[1] has recently shown, however, a mean change of 1.3 mg. per 100 ml. in serum uric-acid levels and of 200 mg. a day in uric acid output by gouty patients kept for short periods first on a lacto-vegetarian low-purine diet (about 0.2 g. purine nitrogen a day) and then on high purine diets (0.5 g. purine nitrogen a day). Although this difference is not very big, it would seem wise to restrict the intake of the more obviously "purinogenous" foods such as roe, kidney, liver, and sweetbreads. Colchicine is as useful as ever in the acute attacks; it is usually given orally, 0.5 mg. hourly until relief or toxicity reactions occur, up to 5 mg. in the first 24 hours. For patients developing undue toxic symptoms, intravenous administration has been advocated by Graham and Roberts,[2] who found that 3 mg. in 3 ml. of saline produced relief within six hours in 30 out of 33 patients. A.C.T.H. by intramuscular or intravenous injection also gives fairly rapid relief, but another attack is apt to follow its withdrawal unless colchicine is then given.[3]

But the gouty patient ultimately derives most benefit from the treatment his physician gives him between attacks, and for this purpose many uricosuric drugs are available. Cincophen, salicylates, probenicid, and phenylbutazone are the most popular; cortisone has also been tried.[4] Of all these drugs the least dangerous and the most effective is salicylate. Jennings in 1937[5] maintained that salicylates give satisfactory control between attacks, and, although Bauer and Klemperer[6] found long-term therapy ineffective, Jennings's results have been confirmed and amplified recently by Marson.[1] With continuous administration of salicylates, 6–7 g. per day with sodium bicarbonate, for periods of over a year, serum uric-acid levels decreased to within normal limits, the pain and incapacity of the chronic phase were relieved, tophi and ulcers disappeared, and acute attacks became less frequent and less severe. Radiological signs regressed.[7] Symptoms of intolerance were troublesome initially, but the majority of patients got over this phase. No bleeding tendency was seen, although prothrombin levels fell in some patients. Oral vitamin K, 10 mg. a day, was given for those with a prothrombin time below 25% of normal, and it corrected the deficiency. Aspirin was not as effective as sodium salicylate.

The claims of phenylbutazone and of probenicid have recently been studied in Britain by Mason.[8 9] Probenicid acts on the renal tubules, inhibiting not only the excretion of such substances as penicillin, *para*-aminosalicylic acid, and phenol red but also the transmission of certain substances in the reverse direction. Reabsorption of uric acid from the glomerular filtrate, which maintains normal as well as gouty levels of uric acid, is inhibited, and blood levels of plasma uric acid in gout fall promptly after a single dose of 2 g. and by daily administration may be maintained indefinitely below their previous level, often at 50% of it. As Mason emphasizes, this does not eliminate acute gouty attacks, which may occur when the plasma uric acid is well within the normal range, but the attacks are less frequent and less severe. Probenicid is relatively free from toxic effects, but it is wise to start dosage with 0.5 g. a day to avoid renal concretions. It is to be noted that, if salicylate or aspirin is given together with probenicid, the beneficial effect of each is annulled.[10]

Phenylbutazone has not only an effect in the acute attack, perhaps due to its analgesic properties, but it has also a mild uricosuric action. Given in doses up to 600 mg. a day, it may lower plasma levels, but this effect is often slight. Renal excretion is usually increased unless water retention occurs, but the uricosuric effect does not compare favourably with that of either salicylate or probenicid used for interval therapy. Finally, it has a much greater frequency of undesirable side-effects than either of these drugs.

[1] *Quart. J. Med.*, 1953, **22**, 331.
[2] *Ann. rheum. Dis.*, 1953, **12**, 16.
[3] Wolfson, W. Q., *et al.*, *J. Lab. clin. Med.*, 1949, **34**, 1766.
[4] Anderson, A. E., *Amer. J. Med.*, 1954, **16**, 292.
[5] *Rep. chron. rheum. Dis.*, 1937, **3**, 106.
[6] *New Engl. J. Med.*, 1944, **231**, 681.
[7] Marson, F. G. W., *Brit. J. Radiol.*, 1952, **25**, 539.
[8] *Ann. rheum. Dis.*, 1954, **13**, 120.
[9] *Brit. med. J.*, 1954, **1**, 788.
[10] Pascale, L. R., *et al.*, *J. Amer. med. Ass.*, 1952, **149**, 1188.

TREATMENT OF NEUROBLASTOMA WITH VITAMIN B_{12}

Neuroblastoma is one of the commonest malignant tumours of childhood, and until recently the published results of treatment have been far from encouraging. In 1950 at the Hospital for Sick Children, Great Ormond Street, London, a child with inoperable pelvic neuroblastoma was treated with massive doses of vitamin B_{12} to determine whether this agent could bring about

[1] *Ann. Rep. Brit. Empire Cancer Campaign*, 1953, 174.

any maturation of the neoplastic tissue, since this is a tumour consisting mainly of undifferentiated neuroblasts. Remarkable regression of the tumour was observed. Naturally this success has been followed up, and, in the report of the British Empire Cancer Campaign for 1953[1] preliminary results of treatment of ten cases of neuroblastoma with vitamin B_{12} are described.

Two of the cases received only short courses of the vitamin in combination with surgical removal of the primary tumour and subsequent radiotherapy, so that, although they are alive and free from symptoms after nineteen and twelve months respectively, no assessment of the value of the vitamin B_{12} therapy can be made. Of the remaining eight cases four have shown striking regression of the primary tumour, of metastases, or both. Three of them have now survived for periods of thirty, thirteen, and fourteen months respectively from the onset of symptoms, and the disease process appears to have been arrested. In the fourth, although the ultimate prognosis was poor, there was striking regression of extensive liver metastases over a period of seven months.

When the period of survival in these cases is compared with general observations of duration of survival in fatal cases of neuroblastoma (varying from averages of four or five to eleven months), these results are certainly encouraging. As the authors point out, however, it is necessary to observe the surviving children over longer periods and to extend the observations over a larger series, especially since neuroblastoma, although characteristically a very malignant tumour, has occasionally been noted to undergo spontaneous regression.

As to the possible mode of action of vitamin B_{12} on neuroblastoma, the original idea that it might enhance maturation of the tumour tissue is now thought to be erroneous, since where obvious benefit has resulted from treatment there has been progressive shrinkage of the tumours compatible with destruction rather than differentiation of the tissue. Haemorrhagic necrosis frequently occurs in untreated neuroblastoma, and it is possible that vitamin B_{12}, either by direct metabolic interference or by inducing growth in excess of the available supply of nutrients, may encourage such a necrotizing process.

EPIDEMIC GASTRO-ENTERITIS

A discussion earlier this year at the Royal Society of Medicine showed that gastro-enteritis is being investigated from rather different angles on the two sides of the Atlantic. In the U.S.A. Gordon and his colleagues,[1 2] with the assistance of human volunteers, have carefully worked out the part played by viruses in epidemic gastro-enteritis. They have shown quite clearly that two different viruses may cause this infection. The first, called the Marcy strain, was present in bacteria-free filtrates of faeces collected during an institutional outbreak of gastro-enteritis. After each of seven serial passages the filtrates, given orally, caused the disease in about 66% of volunteers. The experimental disease was similar to the original outbreak, in that the incubation period was about 60 hours and the symptoms were the same—namely, anorexia, nausea, vomiting, headache, and profuse watery diarrhoea, with no fever, lasting about 96 hours. The volunteers were immune to reinfection with the same infective material. What appeared to be a different virus was found in an epidemic of nausea and vomiting in which the incubation period was about 27 hours. Both the naturally infected patients and the volunteers suffered from nausea, vomiting, abdominal pain, and pyrexia lasting about 24 hours, but they had little or no diarrhoea. In neither of these infections could the disease be induced by inhalation or nasal instillation of infective material, nor was there any cross immunity. The blood, urine, and cerebrospinal fluid showed no abnormalities. The clinical description of these diseases is not unlike those of epidemic nausea and vomiting by Hargreaves,[3] Silverton,[4] and more particularly by Goodall,[5] whose patients had symptoms more suggestive of the Marcy type of infection. It is probable that other viruses will be found as the causative organisms of infections common in this country, with general symptoms as well as gastro-intestinal upset. Virus enteritis is not peculiar to man, since scouring in calves may be due to a virus which affects the respiratory tract primarily and the intestine secondarily: there is no evidence one way or the other to show whether these human and animal viruses are related.

In this country special attention has been paid to *Escherichia coli* as a cause of both infantile diarrhoea and calf scours. It seems that it is the young which are particularly liable to this type of infection, whereas adults are for all practical purposes immune. In both babies and calves this disease is highly infectious, although the severity of the symptoms may vary greatly. There is evidence from all parts of the world that certain sero-types of *E. coli* cause gastro-enteritis, and at the meeting at the Royal Society of Medicine Dr. John Smith reported his findings in Aberdeen. Whereas in 1947 specific types were associated with 240 cases of infantile gastro-enteritis in that city, of which 104 were fatal, in 1948 there were 62 cases with 17 deaths and in 1949 78 cases with 1 death. In the succeeding years, up to the end of 1953, 36, 50, 22, and 20 infants with gastro-enteritis were found to harbour specific types of *E. coli*, and there were no deaths among them. Unfortunately the number of *E. coli* sero-types believed to cause the disease are increasing, as has been shown by Taylor[6] and by Smith. Though sporadic cases occur, this is mainly a disease affecting institutions admitting young children of a susceptible age. Investigations by members of the medical staff of the London County Council show that many of the infants believed to be suffering from sporadic infections have been in contact with infected babies, or at least living in such circumstances that there was an increased chance of contact with other babies.[7] Rogers[8] has shown that the sero-types of *E. coli* may be isolated from all the articles round the infected baby, but whether one route of infection is more important than another is not known.

[1] *J. exp. Med.*, 1947, **86**, 409.
[2] Ibid., 1953, **98**, 461.
[3] *British Medical Journal*, 1947, **1**, 720.
[4] *Med. Offr.*, 1952, **88**, 215.
[5] *British Medical Journal*, 1954, **1**, 197.
[6] *J. Path. Bact.*, 1952, **64**, 715.
[7] *Brit. J. soc. Med.*, 1953, **7**, 194.
[8] *J. Hyg. (Lond.)*, 1951, **49**, 140.

SCIENCE AND HUMAN NATURE

DR. ADRIAN'S PRESIDENTIAL ADDRESS TO THE BRITISH ASSOCIATION

The inaugural meeting of the British Association was held in the Sheldonian Theatre, Oxford, on September 1, when the president, Dr. E. D. Adrian, O.M., P.R.S., delivered his address from the chair. He began by glancing back to a former Oxford meeting, in 1880, just after the publication of Darwin's *Origin of Species*, when Huxley and Bishop Wilberforce met in memorable combat, the Bishop holding up to scorn the notion that man and monkey could have a common origin.[1] Within a few years of that meeting, said Dr. Adrian, the battle for Darwin's theory was won, and it seemed then that the discoveries of science had forced men to give up beliefs on which they had relied for centuries. The scars of that controversy were now almost healed, but, whereas our grandfathers were faced with scientific discoveries which for many of them spelt the end of worthy human aims, our own generation faced discoveries which might spell the end of all human aims, whether these were worthy or not.

Atomic Devastation

"We can regret that atom bombs are possible without regretting the discoveries which led to them." Advances in natural science could not avoid advancing methods of warfare, if only by making armies more healthy. Immense explosions and devastation were not the only dangers. Even if these were survived there might remain from repeated atomic explosions a degree of general radioactivity which no one could tolerate or escape. When atomic energy was used for industry due precautions could be taken against radioactive contamination, but in major war such precautions would soon be set aside. A long war between powers well armed with bombs would mean an order of contamination involving both victors and vanquished.

Yet we had no right, Dr. Adrian continued, to think that our predicament was much worse than that of an earlier time. Our grandfathers could do nothing to ward off the danger which seemed to face their cherished beliefs, but our fate was in our own hands. If only we could make our behaviour worthy of our increased knowledge we could live safely. The scientist had a double responsibility. He must apply his science to learn as much as possible about the mental and physical causes which made people behave as they did, and he must study human nature to prevent its failures; but he could not wait for the discoveries which might make people act more wisely, he must "take us as we are" and point out that the human race could not stand more than a few thousand large atomic explosions whether these hit their target or missed it.

Wanted: Clear Heads and Even Tempers

It was some comfort to feel in face of these dangers that increased knowledge could be used for defence as well as attack. To be protected from radioactivity mankind could only live in caves on uncontaminated food and drink; but an increased knowledge of how the mind of man could be influenced would certainly forestall many of the influences which might be used to undermine its integrity. Not that it was very likely that the most detailed knowledge of brain physiology would help mankind much towards living more peaceably; though it would be rash to prophesy, and it would help a little to settle our differences if we had the means of ensuring a clear head and an even temper. But clearly we must look beyond physiology for an adequate picture of the human brain in action.

Dr. Adrian went on to point out how much was already known about human behaviour from our own experience and from the accumulated wisdom of the past. But it was only in recent times that we had tried to check our knowledge by the methods of natural science. The development of physical science dated from the time when direct observation and experiment were accepted as better guides than the principles which had seemed self-evident to the philosophers and schoolmen. In the same way now we could look forward to the many branches of social science to make a dispassionate study of what actually happened in our society without regard to what might be expected to happen if we were to believe all we had been taught.

An Objective Study of Society

It was far easier now than at the time when the British Association was founded a century and a quarter ago to deal with large groups of individuals, and psychologists had far more knowledge of the irrational factors which could sway the smaller groups as well as the family and the individual. "The stage seems to be set, for the new development [an objective study of human society] may well be the most important scientific development of this century. Why are we still so reluctant to think well of it?"

The principal answer was that we are not yet convinced that the kind of observation that the social scientist could make would be sufficiently objective and precise. Those who worked in laboratories had an easier task in selecting what they should observe, though even they found it difficult to select and observe fairly—for example, not to reject the exceptional result as worthless when it did not fit a cherished theory.

The distrust of social science was probably intensified, Dr. Adrian went on, by the layman's tendency to speak of experiments in the social field as though they were comparable with experiments which obeyed the exact rules of the laboratory. But the whole training of the social scientist warned him of the complexity of any situation in which human beings were involved.

At present many kinds of investigation were grouped under the umbrella of social science; the groups seemed to have little in common, and few of them could put their results in figures. But scientists and laymen alike were becoming aware of the value of social investigation and the degree of certainty which it could bring. Everybody could see that there were facts to be found out about social relations, social risks and the like, and that the search for these facts could be conducted on reasonably scientific lines. These large-scale investigations, however, were "too important a plant to be left in the hot-house atmosphere of research institutions and Unesco teams."

The scientific investigation of mankind would help the process of civilization by finding out the weak points in our equipment and suggesting remedies. But these scientific activities would play only a limited part in the development of human society in this scientific age. The power we had acquired over the forces of nature had made it possible to increase mental training as well as standards of comfort. Here Dr. Adrian made a plea for more social scientists in our universities.

The Critical Spirit of the University

Although of the two or three thousand million people in the world perhaps not more than five million were receiving full university training, this number had risen steadily in recent years in spite—or because—of wars. In the United Kingdom there were 85,000 students at the universities; true, only about 1 in 30 of the age group concerned, but a few years ago the figure was only 1 in 60, and there must be many parts of the world where the university was only now beginning to play its part in civilizing the most intelligent citizens.

University students were not usually considered to be the most complacent members of the community. They tended to be critical of those in authority, and long might they

[1] "Will Dr. Huxley tell us whether it is through his grandfather or his grandmother that he derives his ancestry from the venerable ape?"

remain so. If they were not, if they believed all that they read in the official inspired press, or even what they were taught by unrestrained professors of the greatest integrity, there would be little chance of their learning how to use their knowledge for solving the new problems of our time. "It is something to know that there are many more people in the world to-day with brains trained better to deal with their environment by learning how its problems have been dealt with in the past."

". . . The control which has been achieved by science," said Dr. Adrian in conclusion, "has made it possible for us to improve our own natures by more education in the arts of civilized life. We may perhaps improve ourselves more rapidly if we can gain more insight into human behaviour. That is something which the [British] Association can encourage, but it is only a small part of what it must do. It must not cease to encourage every kind of scientific inquiry, for it is human nature to inquire, to learn by experience, and to profit by what it finds out."

Nova et Vetera

GERALD BERTRAM WEBB

1871–1948

The erection by Americans, in America, of a costly university building in memory of a recently deceased English doctor is rare enough to deserve a brief sketch of his medical career, enriched throughout by his wide and varied humanity. The "Gerald B. Webb Memorial Building," erected and equipped at a cost of $150,000, honours the name of Dr. G. B. Webb, who graduated at Guy's in 1893, migrated to Colorado, married a granddaughter of Jefferson Davis (President of the Confederate States in the American Civil War), made an international reputation in tuberculosis research and practice, and died there, full of years and honours, in 1948.

The building — recently opened—forms part of the "Medical Center" of the University of Colorado, and is dedicated exclusively to tuberculosis research, in continuance of the aims and work of the Colorado Foundation for Research in Tuberculosis, established by Dr. Webb thirty years ago. There was a distinguished gathering for the opening ceremonies; the principal speaker was Dr. René J. Dubos, of the Rockefeller Institute for Medical Research, who discussed tuberculosis as a chronic problem for research and also read to the scientific meeting a paper on the chemotherapy of tuberculosis as affected by tissue factors.

Gerald Webb was a native of Cheltenham. His father was a well-known business man; his mother was descended from Huguenot ancestors who came from Rouen to London, rich goldsmiths stripped of all their possessions, during the massacres of 1685. He was educated at Dean Close School, took his M.R.C.S., L.R.C.P. and, for good measure, L.D.S. at Guy's Hospital and M.D. at Denver. While reading at Guy's for his London M.D. he married an American lady, who soon afterwards developed pulmonary tuberculosis. He was advised by London specialists to take her at once to the Rockies, where she died some years later. He then married Varina Davis Hayes, granddaughter of the former President of the Confederacy, who bore him five children and died in 1934. The eldest son, who held a commission in the American Commando Forces, survived the war but was killed in a steeplechase at Baltimore in 1947.

Rocky Mountains Practice

For over half a century Webb practised at Colorado Springs, 6,000 feet up the Rocky Mountains, giving much time to research, especially in tuberculosis, and did stimulating work of pioneer value on the morphology of the blood at high altitudes, the blood picture in tuberculosis, and the production of relative immunity by the gradual increase of small doses of living tubercle bacilli. He rapidly became one of the leaders of tuberculosis research in the United States. From the first he emphasized the supreme importance of rest in treatment, using a special technique of postural rest and mental quietude. In recent years he studied the metabolism of the tubercle bacillus and problems of chemotherapy.

His early practical experience was invaluable, starting with postgraduate work in London under Sir Almroth Wright and at Vienna under Edmund von Neusser. In 1918–19, as a lieutenant-colonel in the U.S. Medical Corps, he was senior consultant in tuberculosis to the American Forces in Europe. Already, in 1912, he had represented the National Tuberculosis Association (of America) at the International Congress at Rome. He was president of that association in 1920–1, when he was instrumental in setting up the first functioning committee on medical research; and he again represented the association at the organization of the International Union against Tuberculosis in Paris in 1920, and at its first conference in London in 1921. The association awarded him the Trudeau Medal for Research in 1939. Meanwhile Colorado College had conferred on him its honorary degree of Doctor of Science in 1936, and the University of Colorado followed suit in 1938. He was President of the American Association of Physicians in 1939.

Literature and Sport

Webb had a considerable knowledge of medical history, with something of the bibliophile's passion, and he loved poetry, literature, and conversation. He was an ardent sportsman and one of the best polo and lawn tennis players in Colorado—a state more than twice the size of England. He had been captain of his school; and at Guy's he got his tennis blue when his team won the inter-hospital cup in the 'nineties. In 1901 he hunted cougar with Theodore Roosevelt, and in 1907 he captained the winning team (Colorado) in the inter-state polo tournament of that year.

Like his father, Webb shone in amateur theatricals and was an outstanding Chancellor in *Iolanthe*. He played good chess and bridge and was a keen botanist, ornithologist, and palaeontologist. Because of his many-sided intellect he was an inspiration to his colleagues and helpers and was able to stimulate his patients in nature study, the arts, and the reading of good literature. Indeed, he always insisted that this aspect of his handling of patients was a vital factor in their cure. His essays on "The Prescription of Literature" and "Prescription of the Scrap Book" were incidental to that principle. He wrote several books and numerous essays, including the most authoritative memoir on Laennec in the English language (1928) and an excellent short history of tuberculosis (1936). He was U.S. delegate at the Laennec centenary celebrations in Paris in 1926.

Though in his last decade he had an aneurysm, which ended his life suddenly in 1948, he made light of it, and remained in active practice and direction of research, interlaced with bird-watching and literary work, to the last day of his life. He enjoyed in unusual degree the affection of all who came into contact with his alert and intelligent encouragement. He is survived by some fourteen children and grandchildren in the U.S.A. and by a brother and many collateral relatives in England.

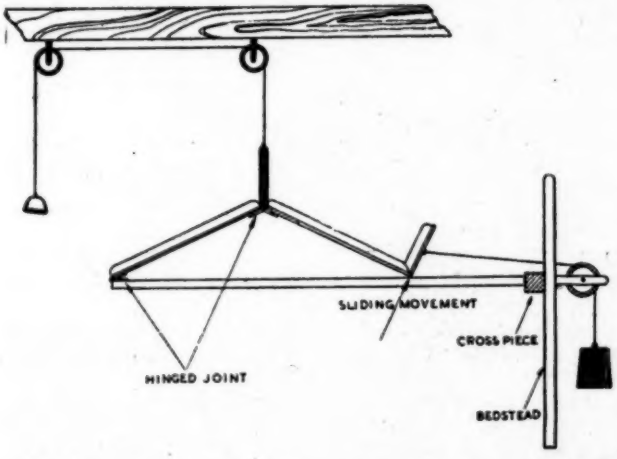
F. W. J. W.

Preparations and Appliances

A SELF-EXERCISING APPLIANCE FOR THE PATIENT WITH HEMIPLEGIA

Dr. MICHAEL D. CASHMAN, house-physician, Sedgefield General Hospital, writes: Rehabilitation of the patient with a hemiplegia is no new problem, and it is one which affects the general practitioner and the hospital medical officer alike. The appliance described here, which I hope may be a new contribution to this problem, has been used at this hospital to advantage. The principle of this apparatus is that the patient, whether completely bedridden or otherwise, is able to exercise his paralysed leg with his good arm. The advantages are: (1) it is easily constructed, and, under the direction of the doctor, could be made in the house by a handyman; (2) it gives the patient the assurance that he is himself making a contribution towards his progress—an important point; and (3) being simple to operate, it does not require the continuous supervision of a trained physiotherapist.

To construct the apparatus, a beam is first erected diagonally across the patient's bed, and two small pulleys are screwed into it—one above the knee of his paralysed leg and one above his active arm. A wooden splint, full-length, lies under the paralysed limb; and a cross-piece is fixed to this to brace it against the foot of the bed.



Riding on this splint is a second splint, hinged at the knee, padded for comfort, and fitted with another piece of wood at the foot, to which is attached a string passing over a pulley at the end of the bed (and attached to the lower full-length splint, so that the whole appliance is one unit), and to this string weights can be attached. The hinged splint is fitted with leather straps by which the paralysed limb is fixed to it above and below the knee. From the hinge of this splint strings pass on either side of the patient's knee and unite to pass up to the beam, riding on the pulleys and ending in a handle which lies accessible to the active arm.

The patient grips the handle and pulls, and by doing this he is able to flex his paralysed limb to well over a right-angle. On releasing his hold the weights suspended over the pulley at the foot of the bed return the limb to the extended position. Once the patient has been fitted to the apparatus, which necessitates only securing the limb by two straps, he can continue with his own exercise for as long as is required without further supervision. As a prelude to more advanced physiotherapy, and in particular in restoring the patient's confidence in his own capabilities, I have found this piece of apparatus a useful contribution.

I am indebted to Mr. R. Alderson, S.R.N., for designing and constructing this appliance, and to Dr. G. B. R. Warnock for permission to publish details of its use in this hospital.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Use of Controls in Clinical Research

SIR,—In your issue of August 14 you publish two articles on the treatment of ulcerative colitis (pp. 376 and 378). In the first, alternate cases are treated by the active agent with "dummy" treatment of the controls, the experiment being so designed that neither the patient nor the physician knows which treatment is being given. The writers of the second article, on the contrary, state that they rejected this method of "blind trial," since "a potentially dangerous substance, to which the individual response of patients varies so markedly, could not be used without the physician in charge knowing exactly what was being given." On this fundamental question of ethics, which of your contributors is right?

Apart from the ethical aspect, how sound scientifically is the increasingly frequent assumption that blind treatment of alternate cases is a good method of control in clinical research? It would seem unlikely that a method which is admirably designed for the large and relatively homogeneous biological populations of the laboratory was also the best method for infinitely varying human beings, treated as individuals and not in the mass, and with infinitely varying disease patterns.—I am, etc.,

London, W.1. DAVID H. PATEY.

The Dumping Syndrome

SIR,—Although there is little agreement about the pathogenesis of the dumping syndrome, nearly all who have studied the problem are agreed about the medical management of those who suffer from it. The most effective measures, however, are not widely known and many patients are made worse by being advised to keep to a diet consisting largely of milk. We recently attended, as British delegates, a discussion on this subject at the International Congress of Gastro-enterology in Paris. Before doing so we made an extensive study of the literature, and received communications from some 50 British physicians and surgeons who are interested in the problem and to whom we had sent a questionary. We wish to take this opportunity of thanking them for their great help. The recommendations which follow are based on the literature, on these communications, on papers read at the Congress, and on our own experience.

(1) The patient should be reassured that he has not got another ulcer and that the symptoms will steadily improve and probably disappear completely. (2) Meals should be taken as dry as possible and liquid foods should be avoided. (3) The size of the meal should be limited to that which the patient can tolerate. (4) Drinks should be taken *between* meals. (5) A careful analysis should be made of the patient's dietary habits to find out which foods cause symptoms, and the following should each be avoided for a period in turn: specific foods which are suspected of being causative; milk and milky foods; sugar; and fats (especially cooked). Meat, cheese, butter, bread, fish, potatoes, salads, and vegetables can usually be taken freely.

The condition is nearly always relieved if food is taken lying down. Those who suffer from bilious vomiting are often relieved if they lie down *before* the meal. Drugs, taken by mouth before meals, may sometimes help. The best are procaine hydrochloride (30 ml. of 1% solution), "xylocaine viscous" (10–15 ml.), hexamethonium bromide (250 mg.), and sodium bicarbonate (a teaspoonful). A posterior bilateral splanchnic block (Kappis's technique) with 50 ml. of amethocaine on each side is nearly always effective temporarily, and sometimes its effect is permanent. Surgical measures (especially conversion to a Billroth I type of

anastomosis) are available to those with severe and persistent symptoms, and usually cause improvement. They should not be embarked upon until at least 18 months after the first operation.

We shall be reporting on these matters more fully in the near future.—We are, etc.,

Bristol. W. M. CAPPER.
Belfast. R. B. WELBOURN.

Intramuscular Iron

SIR,—As a medical adviser to the company responsible for the production of "ferrivenin," I should like to comment upon the letter from Dr. D. Thomas (*Journal*, July 31, p. 303), in which he describes the administration of this material in the form of an intramuscular injection to a patient suffering from iron-deficiency anaemia. Whilst his report is most interesting, I believe that such a procedure cannot be recommended in view of the necessarily highly alkaline *p*H of ferrivenin and the distinctly irritant effect which such a solution may exert upon tissues with which it may come into contact. I am indeed pleasantly surprised to read that discomfort was "transient and minimal"; I should have expected the reverse to be true.

Previous investigations which have been carried out upon this specific subject have demonstrated the fact that saccharated oxide of iron is, in fact, unsuitable for intramuscular injection in terms of both absorption and tolerance; and, while it is not desired to question the accuracy of Dr. Thomas's observations, it is obviously desirable that the existence of such contradictory evidence be stated. I may say that the makers themselves cannot recommend such a procedure, and indeed do not wish to be associated with any report supporting its adoption. Of recent years a considerable amount of work has been carried out upon the problem of iron administration by the intramuscular route, and it is hoped that in the near future this work may culminate in the provision of a satisfactory preparation for this purpose.—I am, etc.,

Holmes Chapel, Cheshire. W. M. FEE, Benger's Ltd.

SIR,—Having read Dr. David Thomas's letter (*Journal*, July 31, p. 303) and Dr. R. F. Jennison's letter (*Journal*, August 21, p. 464), I am prompted to relate my experience with intramuscular iron. Last year I was working in a hospital in West Africa where, among other duties, I had to see approximately 60 patients at a morning surgery. Some of these needed parenteral iron (many of them also received iron in some form orally). At first I tried giving them "ferrivenin" intravenously, but I soon discovered that I could not spare the time to give it intravenously, so I started with small amounts deep into the buttocks and gradually increased the quantity to 2 ml. It caused a certain amount of pain, but nothing more than many specific intramuscular injections do. On an average I gave 15 ml. of ferrivenin each morning. None of the patients developed any local reaction.

With regard to Dr. Jennison's remark about "the painful reaction that can occur due to accidental extravenous injection," I would like to say that there is a big difference between giving subcutaneous and deep intramuscular injection. Subcutaneous injection of crystalline penicillin can cause an abscess. I do not advocate routine intramuscular iron, but occasionally there is a place for it.—I am, etc.,

Rochdale. D. GEANEY.

Frost-bite by Accident

SIR,—The following report is of an accident which, to the best of my knowledge, is unique—a case of frost-bite caused by an apparently empty nitrous oxide cylinder.

The patient was undergoing a prolonged (three hours) ophthalmic operation, under nitrous oxide, oxygen, and trichlorethylene anaesthesia, using the Bullough's T-piece technique, the rates of flow being 8:3 litres of N_2O and O_2 respectively. During the operation a full cylinder of gas was started and, in due course, exhausted. It was removed from the machine and replaced by a fresh cylinder. The used cylinder was left standing on the floor wide open to ensure complete exhaustion, and the hissing ceased after a few minutes. Shortly after this the surgeon passed a drainage tube into the nose, a procedure involving the removal and replacing of towels, connexions, etc., and taking the best part of half an hour. Afterwards the operation card was brought up to date.

By this time there could be no doubt about the emptiness of the cylinder, although there was still a thick layer of frost over the lower quarter. Intending to return it to the empty cylinder rack, I picked it up by the neck with, as was afterwards painfully evident, the outlet covered by my palm. I want to emphasize that even this intimate contact failed to detect any flow of gas whatever. The corridor contained some trolleys, and, to avoid them, I swung the cylinder up, intending to carry it inverted. Immediately it was upside down, however, there was a forceful rush of gas of such violence that I feared it would tear the skin. Contact lasted no longer than it took to drop the cylinder, but there remained a dead white area of skin covering the lateral half of the palm and flexor surfaces of the proximal phalanges of the thumb, index, and middle fingers. "Vaseline" gauze and a pressure dressing were applied in a few minutes, by which time the area had become reddened and patches of erythema were seen on the other fingers and the lateral part of the forearm. When the dressing was removed on the ninth day, it was seen that there were second-degree burns of the entire palm and of the flexor surfaces of the thumb and index finger, sparing only the tips. The rest of the palm and the distal forearm suffered only first-degree burns. A second dressing was applied, and a complete and uneventful recovery followed.

The mystery is how sufficient gas to cause such an injury could remain in an open cylinder without giving any indication of its presence. The only partially feasible explanation seems to be that the rapid flow of gas caused such a degree of cooling, indicated by the persistent thick layer of frost, that a layer of dense gas, if not liquid N_2O, remained at the bottom of the cylinder. Such a layer would be protected by a temperature and pressure gradient up to the outlet, which would be at room temperature. When the cylinder was inverted, this layer ran down into the warm upper part, where it rapidly expanded, being forced through the outlet fast enough to cause sufficient cooling to freeze the hand. To add to the incredibility of this explanation, I have twice inverted cylinders which had been exhausted at the same rate and obtained no flow at all. If anyone can advance a more likely explanation, I should be very interested.—I am, etc.,

Ottawa, Canada. HAROLD T. KAY.

Arterial Embolism

SIR,—The medical memorandum on "Sudden Simultaneous Arterial Embolism Involving all Four Limbs," by Dr. C. D. Alergant (*Journal*, July 10, p. 86), which has just reached me recalled a case of embolism involving both lower limbs during my first house post.

The registrar and I had just entered the ward on the start of a round, when a woman of about 50 complained of sudden severe pain in both legs. She was under treatment for congestive failure precipitated by acute bronchitis, and had mitral stenosis with auricular fibrillation. On examination she was shocked and both legs were turning white. No pulsation could be felt on either side in the femoral artery and there was no pulsation below this level. The patient was transferred to a surgical unit, where a successful embolectomy from the bifurcation of the aorta was performed three hours later. Circulation was restored to the limbs, but unfortunately she succumbed to a further embolic episode within 24 hours. As far as I can recall, there was no suspicion of subacute bacterial endocarditis and the source of the embolus was presumably the left auricle, although normal rhythm had not been detected.—I am, etc.,

Selangor, Malaya. R. M. MELVILLE.

A Mouthful of Wire

SIR,—The letter from Miss Mabel E. Carter (*Journal*, August 7, p. 361) asking for opinions on the desirability of orthodontic treatment in school-children prejudges the issue by its tendentious tone and might well provoke an acrimonious debate on the whole subject unless ruled out of place in a medical journal.

May I, as one having a foot in both camps, medical and dental, endeavour to answer the question whether treatment is medically justifiable? Generalizing is impossible, but in a great many cases failure to correct deformities may saddle the child with a permanent disfigurement which at best is a source of constant mild regret and at worst may be a severe psychological handicap. On the physical side, though these irregularities do not often hinder mastication seriously, they may, and often do, lead to premature loss of teeth either from direct trauma when incisors impinge on the gingivae of opposing teeth, or from gingivitis leading to pocketing and the usual sequelae. As regards the specific disadvantages mentioned, Miss Carter's experience must be exceptional or her case overstated. The average appliance does not "afflict" the child. It is common for a young patient, inspired no doubt by the competitive spirit, to express a lively hope that a plate will be necessary, and equally common for him to feel unnatural and even uncomfortable when not wearing it. Only in a minority of cases does an appliance affect speech for more than the first few days of wearing it. Eating in some cases may be impeded during a short stage of treatment where the act of biting is utilized to produce tooth movement, but most appliances which would interfere may be taken out for meals, and no fixed apparatus if properly designed should hinder mastication.

The frequent adjustments referred to are presumably those carried out by the child; these are necessarily extremely simple, effected in seconds and at regular stated intervals. Adjustments carried out by the orthodontist are only frequent in exceptional cases; obviously no dentist would wish to bring the child from school to his surgery if it could be avoided. Wires do break, since the need for gentle pressure requires that they shall be slender, but this is not in my experience a frequent mishap, and in only a minority of such cases is there resulting discomfort necessitating an emergency visit. Only too often such breakages are only discovered by the dentist at the end-of-term visit.

In short, though all the horrors enumerated by Miss Carter *can* occur in isolated cases they are not necessary hazards of treatment and taken in the mass they are exceptional, especially now that an increasing number of cases is being treated by the Andresen appliance, which is suitable for several varieties of irregularity, is worn at night only, has no delicate parts to bend or break, and places no strain on child or teaching staff. As a postscript I might add that I have just shown Miss Carter's letter to the mother of a patient, and her only comment was that the irritable and tearful children mentioned would probably be types who would have been so in any case.—I am, etc.,

London, W.1. N. J. AINSWORTH.

SIR,—Some sympathy must be extended to Miss Mabel E. Carter (*Journal*, August 7, p. 361) as the headmistress of a boarding-school in her difficulties with those pupils who are wearing orthodontic apparatus. To some extent the problem is more peculiar to this country than in any other, because in our educational system we make greater use of the boarding-school, many of them being in rural areas far from dental facilities. A headmistress is therefore *in loco parentis* for some nine months of the year.

The fact that a child has irregular teeth means that their positions are the visible manifestation of errors in bone development even to the extent of actual deformity. The object of undertaking orthodontic treatment is an attempt to produce a functional oral cavity, thereby reducing the risk of dental caries and paradontal disease. It must not be forgotten also that for psychological reasons—and these certainly apply to a woman—aesthetics are important. Whereas the dentist is attempting to influence dental development, the headmistress is concerned with mental development, and she is naturally irritated with anything which disturbs the school routine. Miss Carter, in her position, must accept the fact that regular adjustments of apparatus are almost always necessary, but she may recently have had the misfortune to have had charge of certain children discovered after the fitting of appliances to be "breakers." Such patients have a remarkable facility for damage and loss.

Orthodontic treatment is not a "new craze," neither should it be considered an "affliction" on the child. It must be viewed within the general picture of prevention, control, and repair of child dental health. It is recognized and appreciated by the dental profession that the interest and care of the teaching profession in dietetics and development during the dental formative period is invaluable to the dental future of the adult.—I am, etc.,

London, W.1. PHILIP G. CAPON.

*** This correspondence is now closed.—ED., *B.M.J.*

Chlorpromazine and Jaundice

SIR,—The toxic effects of chlorpromazine upon the liver (without actual jaundice), recorded by Garmany *et al.* in their article (*Journal*, August 21, p. 439), are of particular interest to me, for two patients in this practice, while taking chlorpromazine, developed manifest jaundice.

A man aged 56 years, suffering from an anxiety neurosis, was given "largactil" 100 mg. daily. After 22 days' treatment he suddenly developed pyrexia, reaching 102° F. (39° C.) and over, which continued for four days. On the fifth day his temperature subsided to normal, and at the same time jaundice became apparent and persisted for three weeks. Another patient, a woman aged 66 years, who was under the care of Dr. A. J. K. Wilson (my partner) on account of a functional nervous disturbance and was having largactil, reported to him at the surgery with jaundice. She was then apyrexial, but it is not known whether there was pyrexia prior to the onset of the jaundice. The jaundice persisted for over two weeks.

The drug, which was being taken orally, was stopped in both cases when these untoward symptoms appeared, and both made a full clinical recovery from the jaundice. There was no evidence and no reason to believe that either of these patients had a pre-existing hepatic dysfunction, and the jaundice was attributed by us to drug toxicity or to a coincident infective hepatitis. The former supposition now receives support from the article referred to above.—I am, etc.,

Birmingham, 32. W. M. CHESNEY.

Genetic Patterns in Retinoblastoma

SIR,—I have been struck by the failure of the genetic patterns found in families afflicted with retinoblastoma to fit into any of the experimentally verified Mendelian modes of inheritance. Families have been described which show both "horizontal" and "vertical" patterns of affected individuals.[1,2] Thus retinoblastoma may occur in successive generations, being passed down as though it were a dominant trait. In other instances the trait may be found in several members of a sibship, the parents being apparently unaffected, thereby giving the appearance of a recessive trait. Some families have shown both "horizontal" and "vertical" patterns. Several investigators have postulated that retinoblastoma represents a single dominant gene, which, for reasons as yet unknown, does not always find expression. The latter phrase permits one to invoke somewhat rhetorically the status of a Mendelian dominant.

I have wondered if another avenue ought not to be explored. It is the possibility that the appearance and disappearance of retinoblastoma in families is analogous to the similar behaviour of the bar eye mutation in the fruit fly *Drosophila*.[3-6] This mutation involves reduction in eye size and partial blindness in the affected fly. Although this

abnormality has an exceedingly high mutation rate, it is also characterized by a tendency to revert to normal. The mutation "appears" and "disappears" much as described for retinoblastoma. The bar mutation in the fruit fly depends on the serial reduplication of region 16-A, representing only a small amount of X-chromosome material, which is capable of maintaining itself in the homozygous state. When the bar eye mutation reverts to normal there is a concomitant "unduplication" of the repeated chromatin bands. Thus the high mutation rate found at the bar locus in the fruit fly appears to be due to this "unstable" segment of X-chromosome—a quantitative, rather than qualitative, change in the genic material. This experimentally demonstrated mode of inheritance in the fruit fly may be just as susceptible to human application as the principles derived from peas by Mendel.

Perhaps we should re-evaluate certain human inheritance patterns in the light of the principle of chromosomal reduplication as exemplified by the bar mutation. It would seem profitable to apply this point of view to enigmatic patterns such as are found in families with retinoblastoma. The electron microscope or other technological aids in the visualization of human chromosomes may eventually provide direct objective data.—I am, etc.,

Syracuse, N.Y. LYTT I. GARDNER.

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Child Guidance Clinic

SIR,—Dr. J. Bierer's plea (*Journal*, August 7, p. 362) for research to test the value of various kinds of treatment in psychological medicine will surely be supported by all. The need is certainly great in the field of child guidance, which he specially selects for attention. It is a pity, however, that Dr. Bierer draws his conclusions in advance in his condemnation of the three-member child guidance team. Dr. Bierer does not make it clear exactly what he is criticizing—for example, he refers to "the orthodox child guidance clinic." What, in these days, does he mean by "orthodox"? I should have thought that most clinics have evolved and have adopted methods suitable to the number, training, and interests of the staff available; and surely Dr. Bierer does not deny them some sensitiveness to the success or otherwise of particular methods.

In my experience it is completely untrue to suggest that "in the majority of cases the parents need the treatment and not the child." This is a false antithesis. There are a small number of cases where treatment may be directed entirely to child or parents, but in the majority treatment must be twofold. Few parents require "deep treatment," and therefore the psychiatric social worker may undertake the role with them. In the child guidance clinics with which we in this department are connected there is no rigid division of labour such as indicated by Dr. Bierer. For example, we run a clinic in a rural area jointly with the local education authority, who supply the educational psychologist. She visits all the schools frequently and has many cases referred to her. If the problem is not one of school adjustment, with which she can deal, she refers the case for full assessment by the team, which consists of consultant psychiatrist, psychiatric social worker, and the psychologist herself. Referrals also come from general practitioners, school medical service, hospitals, courts, etc. The psychologist sees every child and so does the psychiatrist. Every parent is interviewed separately by the psychiatric social worker and the psychiatrist. The case is then discussed and if taken on for treatment the particular roles are allocated according to the needs of the child and its parents. Treatment of the child is undertaken by the psychiatrist or the psychologist, and the fact that one is a male and one a female is an advantage when deciding the treatment roles. Treatment of the parents is undertaken by the psychiatric social worker or the psychiatrist.

This arrangement works very well, if we accept as a valid criterion the fact that most cases recover. Like Dr. Bierer, we would prefer to put the question to the test of systematic research, and we hope to be able to do this. Comparative studies of the working of different clinics would be valuable, with special reference to the problems dealt with, the associated family circumstances, the methods of treatment and the results of this. New methods such as those advocated by Dr. Bierer could then be compared with the old.—I am, etc.,

Dumfries. EDGAR MCCOY.

SIR,—I have been interested to see in your columns that Dr. J. Bierer has raised the subject of the relationship between child and adult psychiatry (*Journal*, August 7, p. 362). The time has now come to regard child psychiatry as a stepping-stone to family psychiatry. That this has only come about now is due no doubt to the peculiar development of what has hitherto been known as "child guidance." The movement began in the juvenile court and in work with schools. It concerned itself with the "maladjusted child" and was an ambitious programme of guidance to the child in all his aspects from infancy to adulthood. Burt and Howard,[1] after a careful consideration of the term, defined the maladjusted child as being one "whose adjustments to the recurrent situations of his everyday life are less adequate than might reasonably be expected from a child of his mental age, and whose condition or circumstances therefore require special study and treatment." It is evident from the same paper that education, material, social, moral, physical, emotional, and religious factors could play a part in maladjustment. Indeed these writers go so far as to say: "Children who are maladjusted in one respect are not necessarily maladjusted in others." A child can be emotionally and physically healthy and still be maladjusted. Maladjustment is clearly not a clinical entity. Whilst, on the whole, physical conditions causing maladjustment were separately dealt with in medical clinics it was arranged that the other maladjustments should be dealt with by the child guidance clinics. Weaknesses of this approach are now apparent. It was not possible for any one group of workers to offer such an all-embracing service. It was not sufficiently realized that emotional, and not social, stress gave rise to emotional maladjustment. There was a failure to clarify emotional maladjustment (or neurosis) as an entity. A service based on the school tended to ignore the all-important pre-school child and subordinated the vastly greater importance of the home. Lack of training in adult psychiatry led to difficulties in assessments of the parental disturbances.

Fortunately, salvation has come from another field of development. Psychiatrists working with adult neurotic patients came to find that the genesis of adult neurosis lay in childhood, that the first five years were all-important, that the emotional stress on the child emanated from the parents—and, more recently, that parents emanating such stress were themselves neurotic. From this it followed logically that it was important to treat disturbances as early as possible in childhood and to deal effectively with the disturbing focus of the parental neurosis. Mental ill-health in the child has, like physical ill-health, to be separated off from the other maladjustments. It constitutes a special field wherein clinical problems have to be assessed, handled, and treated by trained personnel, protected and bound by ethical considerations. Thus there has grown up the child psychiatric clinic within the Health Service, based on the home, supplying a community service and concentrating on the pre-school child.

The next step came with the realization of the major part played in the child's disturbance by the neurotic parent. A defect in the existing service was pointed out in the admirable memorandum[2] of the B.M.A. on the maladjusted child. "The treatment of the parent of a maladjusted child is perhaps the least satisfactory aspect of child guidance work

at the present time." Concentration on adults in the family and the total family situation brings us to family psychiatry. For some years we have here evolved a technique for the treatment of the family by giving the psychiatrist responsibility for the treatment of the total situation. The adult or adults are treated directly by him, whilst the child or children are treated indirectly through a play therapist, working under supervision on a week-by-week prescription. In this way it has been possible for the psychiatrist to integrate the treatment of child and adult.—I am, etc.,

Ipswich. J. G. HOWELLS.

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Acute Appendicitis in Childhood

SIR,—The frank and frightening discussion of appendicitis in children by Mr. F. Denis Hindmarsh (*Journal*, August 14, p. 388), in which he demonstrates so well and clearly the dangers of delay in diagnosis and treatment, should serve as a good prod to the hesitant. I am glad to hear that there is "insufficient evidence to suggest that it is possible to make a clinical differentiation of one type of appendicular lesion from another." The general practitioner's differential diagnosis might be crude, but in the case of abdominal disease in a child is necessarily dramatic and decisive.

The pitfalls that delay the diagnosis, so well analysed by Mr. Hindmarsh, can be summarized thus: Appendicitis in children varies very much in signs and symptoms and seldom follows the classical description. There is, however, one constant feature: I have never yet (in 30 years of general practice) seen an appendicitis without *persistent pain*. On the other hand, neither the parent nor the practitioner sees a child suffering from persistent pain after a dietary misadventure (even after a green apple escapade). Therefore persistent abdominal pain in a child should be treated as a danger signal for a complete examination, in the hope of eliciting some of the classical confirmatory signs. Should these, however, be absent, the sole fact of persistency of abdominal pain is quite sufficient in itself to indicate laparotomy for appendicitis, unless some other serious and rarer condition is manifesting itself. The risk of waiting for a second attack of "appendicular colic" in a child, the relapse which occurs, more often than not, away in a scout camp, away from paternal memory and family doctors' records, has led to tragedies.

How long should the pain persist to become significant is a matter decided by appraising the patient, the parents, age, previous history, etc. But any abdominal pain lasting up to six hours by day, or keeping the child awake up to three hours at night, is persistent to me.—I am, etc.,

Bexleyheath, Kent. A. KOBY.

"Serotonin"

SIR,—On reading the paper by Drs. D. W. Woolley and E. Shaw and your leading article on "serotonin," alias hydroxytryptamine (*Journal*, July 17, pp. 122 and 144) it occurred to me that serotonin may play a part in the pathogenesis of migraine, for the following reasons. Serotonin is a vasoconstrictor and is antagonized by ergotamine; vasoconstriction is one of the cardinal features of migraine and an injection of ergotamine has a dramatic effect on the attack; but, to quote Gaddum,[1] "Ergotamine has a therapeutic effect on migraine the exact mechanism of which is a mystery." Perhaps the mechanism is its antagonism to serotonin which, when present in excess, causes the attack. This hypothesis could possibly be tested by assaying serotonin in the cerebrospinal fluid in migrainous subjects and controls, and by trying other antagonists of serotonin in migraine attacks.—I am, etc.,

Harrow Weald, Middlesex. ALFRED LETCHNER.

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Diabetes as the First Sign of Pancreatic Carcinoma

SIR,—I have read with interest Professor Charles Rob and Mr. Rodney Smith's article (*Journal*, August 7, p. 330) on the diagnosis of pancreatic carcinoma, but they do not mention diabetes as its first sign or symptom, nor indeed does any book on general surgery I have consulted. However, this does occur rarely and I have seen it in 12 cases (unpublished). Such patients have shown diabetes as the earliest sign for some 3 to 18 months before the development of jaundice or other pathognomonic signs or operation or necropsy made the fundamental pathology clear. To produce diabetes first the involvement of the pancreas is widespread, and animal experiments show that some seven-eighths of the islet function must be destroyed to produce diabetes. The typical pain described may be a pointer or completely absent even when jaundice develops later. The condition should be suspected when an elderly diabetic, in spite of adequate diabetic treatment, continues progressively to lose too much weight. The sedimentation rate is helpful.—I am, etc.,

London, W.1. R. D. LAWRENCE.

Ocular Discomfort at the Cinema

SIR,—Suffering myself from "ocular discomfort" after watching 3D, I read with great interest your annotation (*Journal*, August 14, p. 404), and I would like to emphasize one factor that may have already been meant by your expression "faulty muscle balance." The well-known reflex of accommodation for near vision consists of two separate coupled acts—namely, the act of convergence, that centres both eyes on the same point, and the relaxation of the suspension of the lens, making it bulge and thus bringing the approached picture to exact focus on the retina. Contraction of the pupil accompanies the latter act.

Watching 3D, the convergence is readily provoked with near objects by the separation of their corresponding images for the left and right eye. The relaxation of the lens, however, which is automatically performed at the same time, proves to be a mistake, as obviously the distance from the observer to the screen, and thus to the picture to be focused, remains the same throughout the showing of the film. The eye has therefore to learn the unusual: to perform convergence without accommodating the lens.—I am, etc.,

Middlesbrough. K. ZOBEL.

Rouleaux Formation Intensity of Plasma and E.S.R.

SIR,—I read with great interest the paper "Rouleaux Formation Intensity of Plasma and E.S.R." (*Journal*, August 7, p. 336), by Dr. S. Lewi and Mr. Kevin T. Clarke. This work helps to clarify the significance of the observations of other investigators in this field and should help to reinstate the original Westergren method as the method giving readings which correspond best to the clinical condition of the patient.

In this paper, the writers misquote the conclusions of my work, the preliminary account of which appeared in the *Journal*.[1] I described a metastable state associated with an inhibition of rouleaux formation in blood with high "rouleaux formation intensity" (R.F.I.) when a solid anticoagulant (heparin or oxalate mixture of Heller and Paul) is used. This inhibition of rouleaux formation causes a greatly prolonged aggregation phase of sedimentation so that if a one-hour reading is taken the E.S.R. *appears* to be anomalously low. If, however, the erythrocyte column in the tube is frequently observed it is found that prolongation of the aggregation phase suddenly terminates, intense rouleaux formation occurs, and then sedimentation proceeds at a rapid rate. If the aggregation phase lasts for, say, 50 minutes, then the one-hour E.S.R. reading would be low, but if a reading were taken after 1½ or 2 hours then the true high "potential" E.S.R. of the blood would become apparent.

I also showed that this phenomenon occurs more readily in deoxygenated blood and that for experimental purposes it can be reproduced by deoxygenating the blood with carbon dioxide (CO_2). This appertains *only to blood collected in solid anticoagulant*—if the blood is diluted the phenomenon does not occur. This explains why investigation in the past,[2–4] using the original Westergren method with diluted blood, came to the conclusion that the state of the oxygenated blood caused no significant change in the E.S.R. The work of Lewi and Clarke shows why the delay in sedimentation of undiluted blood occurs more readily in deoxygenated blood, for deoxygenation causes the erythrocytes to swell and thus to increase the packed cell volume (P.C.V.). In some of my own experiments the difference in the P.C.V. between blood fully oxygenated and blood equilibrated with CO_2 was as much as 6%. This is, of course, unphysiological, though I found differences as great as 3% between oxygenated and venous blood.

Lewi and Clarke conclude from their work that the E.S.R. of undiluted blood is not necessarily proportional to the R.F.I. of the plasma. My own work would lead me to believe that this may be only apparent and not real. Only one-hour E.S.R. readings were taken and the type of sedimentation was not recorded. Had sedimentation been allowed to proceed for longer than one hour, then a very rapid phase of sedimentation might have been observed showing that the one-hour reading did not indicate the true rate of sedimentation owing to prolongation of the aggregation phase. The curve for undiluted blood in Fig. 2 (*a*) shows two maxima and minima. As only six readings were recorded this cannot be regarded as a true "curve." Might not this peculiar "curve" be due merely to anomalous one-hour readings?

The full account of my work will be published shortly in *Acta Medica Scandinavica*.—I am, etc.,

Enfield, Middlesex. McD. DUXBURY.

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Contamination of Injection Solutions

SIR,—The contamination of injection solutions packed in multi-dose containers has rightly been brought to wider notice recently. It will indeed be interesting, as Drs. M. Klein, E. G. Millwood, and W. W. Walther report (*Journal*, August 14, p. 411), to read their paper, awaiting publication, on the maintenance of sterility in solutions to be used as eyedrops. The *British Pharmacopoeia* defines substances to be used as bacteriostatics in injectable solutions (of which chlorocresol 0.1% is, of course, one). Similarly the *Codex* has a monograph for a preservative solution for the preparation of eye drops. However, care must be taken in the choice of bacteriostatic, since they are not always compatible with all medicaments—chlorocresol, for example, is not so with benzyl penicillin, and in this instance phenylmercuric nitrate in a strength of 0.001% is probably the bacteriostatic of choice.

To my mind, however, there is another aspect of the presentation of injectable solutions in multi-dose containers which I feel should receive much closer inspection. The *United States Pharmacopoeia*, like that of this country, lays down specifications as to quality of glass, etc., but in addition limits the number of doses in such a container to not more than ten. This is a step which should receive more encouragement here, and possibly official recognition. A bottle of local analgesic solution recently sent to me contained over 30 doses, and the possibility of contamination, both bacterial and with foreign particles, in the final dose may well be very great. This is borne out in the light of Drs. Thomas and Marks's statement (*Journal*, July 10, p. 88) that little bactericidal action was observed over a period of time, using 0.25% phenol as the bacteriostatic in solutions of streptomycin.

The glass ampoule still seems to be the most satisfactory container for injection solutions in so far as the risk of bacterial contamination is concerned, and I am sure that, generally speaking, hospital pharmacists are fully mindful of the possibilities of contamination of their products and are presenting a minimum number of injection solutions in multi-dose containers. The question of the preparation of antibiotic solutions for injection, from the soluble powder, is perhaps best left in the hands of the hospital pharmacist, and I am sure that discussion between him and the medical staff will satisfactorily resolve this problem.—I am, etc.,

Manchester, 20. D. ETCHELLS.

Heart Cases on Cruises

SIR,—Why should Dr. Bernard Myers (*Journal*, July 31, p. 302) be appalled that deaths occurred on his cruise? During the last three or four years, since passages became available to all after the long war interval, large and increasing numbers of elderly people have been travelling, undeterred by their ailments. Some are on holiday trips; some are going to visit or live with sons or daughters settled in Dominions; some want a last look at the old country.

When there are hundreds such aboard it is statistically inevitable that a few should die, and more fall ill. If they die, they have lived enjoyably to the end; burial at sea costs nothing, and is, in my opinion, much pleasanter than burial in some repellent suburban cemetery. If they fall ill, they have a better time in the ship's hospital, and are better fed and better looked after than in any ordinary hospital or nursing-home ashore. The motives of some doctors who tell some patients that a voyage will do them good are not, I think, wholly pure. But who can blame them for wishing to be free of tiresome cases for some weeks or months?

I can assure Dr. Myers that surgeons on big ships regard cardiac deaths and full hospitals as mere routine. Their real worries are smallpox; epidemics of typhoid or gastro-enteritis; borderline cases of mental disorder; doubtful abdomens; mysterious vanishings over the side; and the like. It is seldom a voyage passes without some of these things. So both for their own sakes, and as a ship surgeon (to whom they pay fees) and a shareholder in shipping companies, I welcome all these old people. It is something that Dr. Myers appears to have realized that we of this little-known and rather despised branch of the profession are not just escapees whose life is one long paid holiday.—I am, etc.,

Bristol. G. L. ALEXANDER.

Selection of Medical Students

SIR,—It has been said with truth that the onlookers sitting on the fence see most of the game and are best able to appreciate what is really happening. As an old retired clinician, who has had many students through his hands, I have read with interest and with no little concern the articles of your correspondents in the educational number of your *Journal* (August 28). It is always easier to make adverse criticisms of a policy than to offer concrete suggestions for its improvement, but I cannot but feel that our present difficulty in the selection of suitable recruits for the medical profession arises from a failure on the part of the responsible authorities to recognize those first principles of which their predecessors were so much more cognizant, even as far back as the Middle Ages, when medicine was largely empirical and lacking the precision with which modern science has made us familiar.

In a leading article in the *Practitioner* of February last (p. 121) the writer remarks that "the State educational system of the country to-day is one of the most tragic examples of what happens when quality is sacrificed to quantity." Surely, Sir, this is the crux of the matter. You yourself have emphasized the point in your comment (p. 501) on Dr. D. Brinton's trenchant reminder (p. 483) of the

deterioration in the motives of those who present themselves as candidates for a career in the medical profession. He does but reiterate the view of all true educationists when he points out that personality cannot be measured by standardized intelligence tests, nor indeed by any method which does not ultimately depend upon human judgment. The truth is (and I am by no means alone in emphasizing this point) that the chief defect in most of the recruits for our profession to-day is the lack of an adequate standard of general education. I am fully aware of the practical difficulties and disadvantages which confront those who still dare to advocate a preliminary grounding in the humanities, and to insist that the essential purpose of a university is the pursuit of learning for its own sake. Nevertheless, it can hardly be denied that the deterioration in type of applicants for entry to the medical schools has increased *pari passu* with the tendency to cut short the general school curriculum in favour of early specialization, a tendency which, I regret to say, has been fostered to some extent by the older universities ever since they ceased to insist upon some measure of classical learning as a *sine qua non* of graduation.

Medicine has always been, and still is, a vocation, and until our educational authorities are willing to make some attempt to revive this elemental conception I can see no real prospect of maintaining those traditional values upon which the reputation of British medicine has rested for many centuries, and which now seem to stand in some jeopardy, a danger of which most of your correspondents appear to be painfully aware.—I am, etc.,

London, W.1. MAURICE DAVIDSON.

Scrotal Incisions

SIR,—In a case of hydrocele the tunica vaginalis was excised through a scrotal incision. Subsequently, much discomfort, often amounting to sharp pain, was felt in the wound because of the pull exerted on the sutures by strong, irregular contractions of the dartos muscle. A mild infection of the wound also occurred along one of the sutures. This was probably due to mobility of the wound and intermittent tension on sutures. I am not sure whether activity of the dartos muscle is adequately recognized as a cause of pain in the wound after scrotal incisions, at least in those subjects in whom this muscle is known to be unusually active. In such subjects an inguinal incision would be preferable.—I am, etc.,

Singapore. A. MOHIUDDIN.

Danger of Surf-bathing

SIR,—The lack of facilities to remedy the danger of surf-bathing is a scandal. An Australian expert on this subject states that only three adequate rescue lines are available in this country, let alone such equipment as suggested by Dr. C. Langton Hewer (*Journal*, August 7, p. 358). Let us learn from Australian experience in this matter and follow the lead offered us from Australia House. They are willing to train and help us to equip adequate rescue teams, but their generous offer has been mostly rejected in this country.—I am, etc.,

London, W.1. MICHAEL ASH.

Measuring Circulation Time

SIR,—Dr. A. Gee discusses an interesting method of measuring the circulation time (*Journal*, August 21, p. 446). It is important, however, in choosing patients for his purpose to exclude those who may suffer from peripheral vascular disease. I remember one patient who suffered from intermittent claudication. In his case there was an interval of 13 seconds (Dr. Gee's maximum normal "foot-minus-arm" time) between fluorescence in a skin weal raised over one knee and one raised on his big toe. In fact there was a 20-seconds difference in the times taken by the fluorescein to reach the two big toes. This demonstrated dramatically which leg was the worse, but actually gave little information in addition to that gleaned from the patient's history.—I am, etc.,

Norwich. F. C. RUTTER.

Varicocele and Male Subfertility

SIR,—Dr. J. K. Russell (*Journal*, May 29, p. 1231) in his original article specifically states that "only in those cases in which there was palpable and visible enlargement of the pampiniform plexus was a diagnosis of varicocele made." He goes on to deprecate surgical treatment of the condition. Dr. H. A. Davidson (*Journal*, June 12, p. 1378) accepts these findings, but advocates surgery, and says "as much as possible of the varicocele is excised." Thinking that this treatment was rather drastic for a condition which tends to spontaneous cure, I ventured a mild protest (*Journal*, July 24, p. 241) and am now taken to task by Mr. Howard Hanley (*Journal*, August 14, p. 413) for supposing that he removes the pampiniform plexus. How many people reading this correspondence could come to any other conclusion? Speaking as a general practitioner with 30 years' experience, I have not advocated operation for the condition, but I have seen several cases who had been operated on. I was not impressed. In conclusion, if the subfertility is due to heat, as it may very well be, cooling can be carried out in easier ways.—I am, etc.,

Shipley. H. S. RUSSELL.

Ring Incorporated in Finger

SIR,—If Dr. I. J. Macqueen (*Journal*, August 21, p. 471) will try the experiment of winding twine from the base to the tip of one of his own fingers, he will find how uncomfortable this is, due to engorgement of the fingertip with blood. I, too, have used his method with success, and to the gratitude of my patients, but the twine should be fixed first at the fingertip and wound proximally, the long end being passed last. In the absence of an aneurysm needle, a large darning needle passed eye first under the ring is quite as effective.—I am, etc.,

Acle, Norfolk. J. F. FILBEE.

SIR,—The method of removing a ring from the finger described by Dr. I. J. Macqueen (*Journal*, August 21, p. 471) has been successfully used several times at Chase Farm Hospital. Oedema may be a great difficulty, however, and I do not think the method will always succeed "no matter how oedematous the soft tissues may be." A refinement in these difficult cases is to reduce the swelling by injecting 1,000 Benger units (200 viscosity reducing units) of hyaluronidase ("hyalase") in 1 ml. of 1% procaine, and then massaging the finger. I believe many rings have been cut off unnecessarily in jewellers' shops in the past. This piece-of-string trick has now been made known to jewellers (*The Watchmaker, Jeweller and Silversmith*, October, 1953, p. 100), and it is hoped that they will use it or refer the patient to hospital for it.—I am, etc.,

Enfield. C. ALLAN BIRCH.

Hospital Treatment at Home

SIR,—In recent years much has been written in criticism of general practice, so it is indeed a welcome change to read Dr. James M. Stalker's paper (*Journal*, August 28, p. 512) in which he makes some timely suggestions with regard to the general practitioner's need for better facilities for special investigations, and his place in medical education. All who are interested in raising the general practitioner's status should press for the immediate provision of direct access to ancillary examination facilities at hospital everywhere, and also to make available in the patient's home investigations enumerated by Dr. Stalker.

But the doctor's responsibility to his patient does not end with the confirmation of the diagnosis. The general practi-

tioner is able to look after his own patients provided that he has the time, and he should be encouraged to treat them as long as he feels competent to do so. In those patients requiring treatment where a "special technique" is used, as for example in surgical procedures, then of course it is necessary to refer them to the appropriate specialist for this stage of the treatment, after which he should return to his own doctor's care—if necessary under continued supervision by the specialist. In those conditions where the general practitioner requires expert advice or guidance in order to continue treating his patient he should refer him to a consultant. At present, however, the National Health Service is centred on the hospital service. This is wrong—and extremely costly. Of the large number of patients admitted to hospital for investigations or treatment, and the many more seen in the out-patient departments, a considerable proportion of them could have been treated by their own doctors.

In my opinion, the aim of the general practitioner should be to treat his own patients whenever possible, and to keep patients away from and out of hospitals except when treatment by special techniques or consultants' opinions are required, except, of course, for their attendance for special investigations in the pathology and *x*-ray departments. By this means the practice of medicine is interesting and worthwhile, the patient–doctor relationship is good, and the status of the general practitioner high, so that he can feel that he really is what has so often been written and said about him —"the backbone of the profession"—and not merely a digit pointing the way to the nearest hospital.—I am, etc.,

Hampstead, N.W.3. PHILIP HOPKINS.

Why Be a Doctor?

SIR,—Sir Zachary Cope's review, "Why be a Doctor?" (*Journal*, August 21, p. 453), reminds me of a Bart's classic which might amuse your readers.

One afternoon we were doing a round, on which a very elderly medical student was present. Something prompted the surgeon (Alex Roche, I think) to say to him: "Tell me, Mr. Jones, what made you decide to become a doctor at your time of life?" "Well, Sir," came the answer, rather sanctimoniously, "I thought I would like to save a life before I died." "Good God, man, why on earth didn't you join the fire brigade?" was the retort.—I am, etc.,

Harrow. J. E. S. STEPHENS.

Design of Operating Theatres

SIR,—Operating theatres are usually designed by those who do not work in them, assisted by those who have not had much experience in the business. As a result, they tend to become a manufacturer's paradise of cupboards, lights, and gadgets, without achieving the basic needs of airiness, simplicity, and silence. Paper plans and the prospect of a new theatre are so attractive to the surgeon that it may not be until it is built that he finds that he cannot gown without touching the wall, or hear for extraneous noise. Twin operating theatres with their ancillary rooms cost well over £50,000 to build, and, now that uniformity of plan is likely to extend throughout the hospital world, it is surely time that consideration was given to means to cutting the cost of construction and effecting improvements in design.

The problems of heating, lighting, and ventilation are closely bound to the size of the operating room and the number of its communicating rooms and doors. The remote siting of sluice rooms and sterilizing rooms would bring a tremendous boon of silence in the operating room, if the difficulties of communication and conveyance could be overcome. The use of some rubberized or other material instead of tiles on the walls and floors would minimize condensation and reduce the noise; it might also reduce the cost. These and other aspects of the problem, which are not likely to be solved by individual hospitals, come readily to mind, and I suggest, Sir, that the Ministry should be invited to study the matter on a national basis so that lessons which are learned from experience may be incorporated in future plans.—I am, etc.,

Blackpool. D. K. LENNOX.

Foreign Body in Urethra

SIR,—Recently we admitted to hospital a boy who had been seen by his own doctor because of vague abdominal pain. The doctor could find nothing to account for his symptoms, but after considerable persuasion the patient confessed to having pushed a pencil into his urethra seven days previously. From the time of his misbehaviour to the time of his examination he had suffered very little distress and had passed urine easily.

The patient was a boy of 14 years who seemed to be rather morose. Abdominal examination revealed nothing abnormal. The penis was flaccid, but it was possible to palpate a hard object in the perineum just behind the scrotum. At operation an incision was made in the perineum directly on to the foreign body, which was easily removed by gentle traction with a forceps. The pencil was 6 in. (15.2 cm.) long, ⅜ in. (9.6 mm.) in diameter, and had passed well into the bladder. Recovery was uneventful and the posterior urethrotomy closed in four days without sepsis.

I think the case is of interest because of the age of the boy and the size of the pencil, which, though straight, had successfully negotiated the posterior and prostatic urethra to enter the bladder; further interesting points being the absence of sepsis, though I am sure the pencil was far from aseptic at the time of introduction, and the ease with which the patient could pass urine while it was *in situ*.—I am, etc.,

Mullingar. J. GALLAGHER.

Irreversible Coma

SIR,—During the past three years I have attended over 30 irreversible comas, 19 of these being in the present hospital in the last 12 months. The accepted definition of irreversible coma in deep insulin treatment of schizophrenia is that quoted in the excellent textbook on the subject by W. Sargant and E. Slater[1]: "This is a dangerous complication in which unconsciousness persists despite the giving of adequate intravenous glucose." By experience I have found the repeated injection of 300 ml. 33% glucose intravenously every two hours, plus rectal drip of 5% glucose in saline, and warm blankets in bed gives, in nearly every case, recovery in two to six hours. Only one coma lasted 30 hours, and I think the reason for this was that the above treatment was not given immediately. In one very restless case ¼ gr. (16 mg.) of morphine by subcutaneous injection was used, and in two cases oxygen was used for less than five minutes. It was not necessary to use nikethamide as cardiac stimulant in any of these cases. On a few occasions 10–20 ml. of 10% calcium chloride intravenously was used without evident result, and nicotinic acid 25–30 mg. intravenously, which gives marked vasodilatation but has small influence on interruption of coma.

All except two patients returned to deep insulin coma treatment after one to seven days' rest, and four patients had a second irreversible coma at varying stages afterwards. There was no fatal accident during these emergencies, and patients showed mental improvement or recovery, so that all but four patients were successfully discharged from hospital. I think that the risk involved in long coma and possible accidental irreversible coma can be justified by better results. The term "protracted coma," used more often in America, is perhaps preferable to the term "irreversible coma," which is psychologically discouraging.—I am, etc.,

Newcastle-upon-Tyne. J. S. BISKUPSKI.

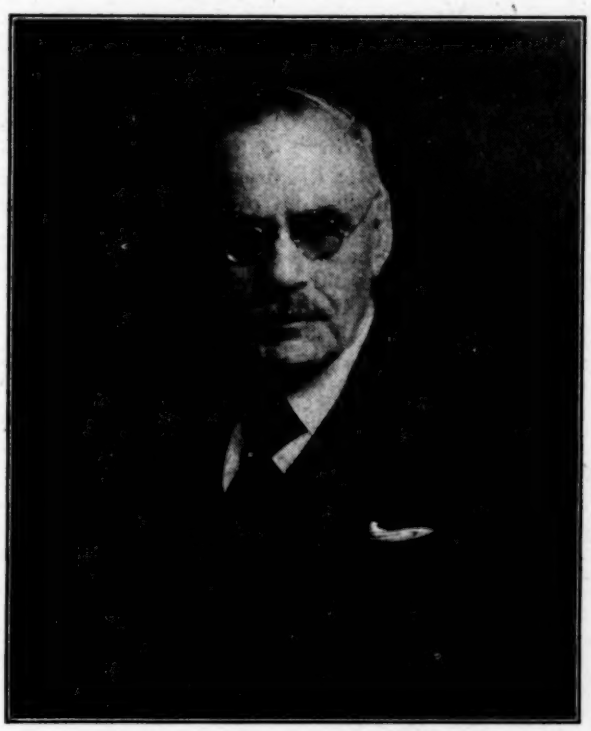
REFERENCE

[1] *An Introduction to Physical Methods of Treatment in Psychiatry*, 1948, p. 37. Edinburgh.

Obituary

ALFRED COX, O.B.E., M.A., LL.D., M.B.

A man greatly loved and honoured in his profession, which he served with lifelong conviction and enthusiasm, even into old age, has passed from us in Alfred Cox, who died on August 31, aged 88. His period as Medical Secretary of the British Medical Association dated from 1912 to 1932, but before that he was for four years Deputy Medical Secretary, and long before taking up any official position he was conspicuous in the North of England in the controversies which took place concerning the constitution of the Association and the conversion of it into a democratic machine, equal to the tasks of the years which lay ahead. After his retirement his energies spread themselves in many channels, but he was at no time happier than when rendering some service to the Association or recalling his early memories of it. Only a short while ago we were privileged to publish his reminiscences of the first Annual Representative Meeting, held at Swansea in 1903.



[*Walter Stoneman, London*

Alfred Cox was born at Middlesbrough on May 5, 1866. In his early childhood his family moved to Darlington, where he had his schooling. He was at first destined for the teaching profession, but an illness in early life diverted him from that calling, and he read for the Civil Service. He was attracted, however, to medicine, and a Dr. Abbott, of Carlisle, persuaded him to become his dispenser and bookkeeper, with liberty to study for his preliminary medical examination in his leisure hours. His leisure hours, however, were few. In the *British Medical Journal* of January 7, 1950, Cox gave an absorbing account of his early experiences—an account which he expanded in his autobiography *Among the Doctors*, published later in the same year. The employment of unqualified apprentice dispenser assistants was afterwards forbidden by the General Medical Council, and many of them no doubt were grossly exploited, but Cox, a lad of 18 at the time, did not know that some of the methods which his chief employed in conducting his practice were frowned upon, and economic necessity drove him to accept the job, which seemed as if it might eventually lead up to the practice of medicine. Meanwhile he slept on a camp bed in the place where the drugs were stored. The dispensing was not difficult, because most of it was from about twenty stock prescriptions. He also assisted his chief in midwifery cases. In those days the reputation of a general practitioner was largely built upon midwifery—a very different state of affairs from that which obtains to-day.

Later he joined a doctor at Stockton-on-Tees, where again his principal task was dispensing, with occasional midwifery, but now he was left with plenty of time on his hands, and in due course he matriculated. His next four years were spent at Newcastle-upon-Tyne, again as a dispenser assistant, while taking his student course at the College of Medicine, and in 1891 he graduated M.B., B.S. from the University of Durham and started in practice across the river at Gateshead. His capital was £30, £1 of which was spent on a brass plate and another £1 on a red lamp. Midwifery provided a large part of his practice, and before he left Gateshead he was attending about 200 cases a year.

At Gateshead he remained until, in 1908, he came to London to join the official staff of the B.M.A. Thus the first forty years of his life were passed on the banks of the Tees and the Tyne, with the iron foundries, the shipyards, the coalfields, the railway sidings, and the chemical works as his background. It was for him a period of unremitting diligence and great sacrifice. His practice at Gateshead was large and busy, but poor. He was a good doctor, the ideal industrial doctor, and his experience gave him a love for the working people from whom he himself came. For a time that affection expressed itself in his membership of the Independent Labour Party, but, though his political sympathies changed, his love of the people remained constant throughout his long life. When in 1931 he was awarded the Gold Medal of the Association, the late Sir Robert Bolam, himself from Tyneside, said that among the people up there in the North Cox's name after a quarter of century was still held in great affection.

Soon after starting practice Cox began to feel uncomfortable at the disorganized state of the medical profession. He joined the British Medical Association in 1892, and his first official connexion with headquarters was his appointment by the North of England Branch to the old Parliamentary Bills Committee, a precursor of the Medico-Political Committee, which in turn was replaced by the General Practice Committee in 1938. He served on the Central Council for two years, from 1901 to 1903. Before that time, however, he had taken a fairly active part in the formation of various local medical societies in Gateshead and other towns in the North. Quite a number of such societies sprang up in the last years of the nineteenth century and the first years of the twentieth for the discussion of medico-political and medico-ethical matters. They were really the result of dissatisfaction with the British Medical Association's record in that sphere of work.

One of these bodies was the Medical Guild of Manchester, which summoned the historic conference in May, 1900, a gathering mainly attended by what now

would be described as the "left wing" of the profession. At the Conference an acute difference of opinion arose about whether another effort should be made to persuade the British Medical Association to assume a representative character, and thus speak for the great mass of practitioners, or whether an entirely new organization should be formed. Cox always recalled with pride that it was he who, after arguing the case for reform within the Association, moved the adoption of a motion which in effect would give the B.M.A. another chance to reform itself. The motion was carried by a large majority, and the result was the setting up by the Council of the Association in 1900 of the Constitution Committee. The Committee reported to the Annual Meeting at Cheltenham in 1901, its recommendations were adopted, and the new constitution came into operation next year. The Representative Body was thus brought into existence, and Sir Victor Horsley, with whom in after years Cox had a great deal to do, was the first chairman. A full account of the circumstances of this change will be found in the *History of the British Medical Association*, published at the time of the centenary in 1932. Cox was a representative at the first and at every Representative Meeting until he took an official position at Headquarters.

When the question of the appointment of a Medical Secretary came forward under the new regime Cox was a member of the Council, and he himself was proposed for the office, along with the late Dr. (afterwards Sir James) Smith Whitaker. But though he regarded this appointment as the very height of his ambition he withdrew his nomination, feeling that Smith Whitaker, as he said, was the better man, and nobody knew better than he did the magnificent work that Smith Whitaker put into the task of reorganization. He also felt that, in the new chapter which had been opened, his proper sphere of action was in his own constituency rather than in the Council itself.

He then set to work to get the new Divisions in his North of England Branch into working trim. Cox was a man with great faith in the periphery of the Association as well as in its centre. He was always anxious lest local weakness should inhibit central effort. He became the first honorary secretary of the Gateshead Division, and remained as such until 1908. He was also secretary of his Branch from 1903 to 1906, and in 1908 he became its president. This secretarial experience not only prepared him for his major work, but it gave him a special sympathy and fellow feeling towards all the Association's local secretaries, expressed continually in correspondence as well as in the annual Secretaries' Conference (the event of the Association year which he most enjoyed) and on other occasions. For a time he was tempted into other fields of activity, and became a member of the Gateshead town council, but this he gave up because he felt that the B.M.A. demanded all the time he could spare from his practice. In 1908, at the Annual Meeting at Sheffield, he was made Deputy Medical Secretary.

Smith Whitaker and Cox, both North-countrymen, made a good working pair, though in appearance, manner, and temperament they were a complete contrast. They were only three years in tandem when the storm broke and the machinery of the Association so recently established was tested to the utmost for its power to mobilize an effective degree of unity in the profession in order to secure reasonable conditions of service and pay under the scheme of National Health Insurance. The Insurance Bill controversy began in 1911, and was for Cox an exceedingly strenuous and anxious time, still more so when in December of that year Smith Whitaker accepted office under the Government as deputy chairman of the National Health Insurance Commission. Upon Cox fell a very heavy burden, made immeasurably heavier by an atmosphere charged with distrust and reproaches. The fact that friendships which were broken at that time were afterwards reconstructed, and that the unity of purpose of the Association, which was in great peril, was restored, was due to Cox more than to any other one man. He had two great gifts which stood him in good stead at that juncture, the ability to set forth and stand by principles, and the ability to salve friendships. On Smith Whitaker's withdrawal Cox took the acting position, and in April, 1912, he was appointed Medical Secretary.

The thunders of the Insurance Act commotion were still rumbling on the horizon when war broke out in 1914, and that meant another strenuous period for Association Headquarters, though not exacerbated as the previous one had been by personal controversy. The Representative Meeting in 1915 set up what soon came to be called the Central Medical War Committee, to organize the profession in such a way as to help the Government to employ every practitioner able to serve his country in such a manner as to turn his qualifications to the best possible use. Of this committee, which had an extraordinarily delicate and onerous task, Alfred Cox and N. Bishop Harman were joint secretaries. As an acknowledgment of his services Cox was appointed O.B.E. in 1918.

In the quieter years following the war, when the Association was taking an increasingly prominent place in public affairs and also establishing itself in a new house, Cox continued to do some very good work, including his investigation into the conditions of various types of practice in the British Isles. The results of this inquiry, with his comments, always to the point, formed the groundwork for the elaboration of the Association's proposals for a general medical service for the nation.

An episode in his career on which he always looked back with pride was his visit to Canada with the late Sir Jenner Verrall in 1924. As a result of that visit the affiliation of the Canadian Medical Association with the B.M.A. was brought about and the warmth of feeling between the organized profession in Canada and in this country greatly increased. This was seen at the Centenary Meeting, when the Canadian Association's delegates came over to London 220 strong. In 1930, when Cox attended the Annual Meeting of the B.M.A. at Winnipeg, the medical profession there gave him a bronze buffalo mounted on Canadian marble, with an appropriate inscription. He also received the honorary degree of LL.D. of the University of Manitoba. An honorary degree which must have pleased him even more, because it was from his old university—the M.A. of the University of Durham—was conferred on him in 1921 at the time of the Newcastle Meeting. The revelation of his qualities as an imperial ambassador of organized medicine led the Council to send him on another mission in 1925. This was to South Africa, where he went alone, and as a result he was able to announce to the Council that a disunited profession with two separate medical organizations had agreed to sink their differences under the aegis of the B.M.A. The Medical Association of South Africa (British Medical Association) was formed. Twenty-one years

later the South African Medical Association came into being as an independent organization, but it remained affiliated to the B.M.A.

A man of international sympathies, Alfred Cox devoted himself also to the international ideal in medicine. He was one of the founders of the Association Professionnelle Internationale des Médecins in 1925, and attended its meetings for many years, even after giving up the Medical Secretaryship, as the Association's representative. At the age of 60 or so he learned to speak French in order to fill this role more effectively. He regarded the A.P.I.M. with something of parental pride, the equivalent, in his view, of the League of Nations in the medico-political and medico-ethical field. The organization has now developed into the World Medical Association.

In the autumn of 1932, at the age of 66—his tenure of office had been prolonged in order that he might remain Medical Secretary during the Association's Centenary—Alfred Cox retired from the Association's service. His retirement was made the occasion of a presentation, when a large and representative gathering of friends assembled in the Great Hall of B.M.A. House to do him honour. Speeches were made by the President, Lord Dawson, Sir Humphry Rolleston, and Sir Ewen Maclean. A portrait of Dr. Cox, painted by Sir Arthur Cope, was presented to the Association and now hangs in the large committee-room at Tavistock Square in which (though still more in the corresponding room in the old house of the Association in the Strand) he had been accustomed to sit at the chairman's right hand and give the *sotto voce* advice in which he was as adept as in his forthright speaking. An album containing the names of 7,000 friends who had contributed to the testimonial was presented to Dr. Cox, with a cheque for £1,000. In an entirely characteristic speech in response he spoke of the pain of severance from a calling which had been practically his only hobby and had become a part of his existence. But his last words were in praise of his colleagues, the loyalty of his successor, Dr. G. C. Anderson—in whose hands, he said, he was sure the future of the Association was safe—and the devoted service of two personal secretaries. One of Cox's most endearing qualities was always his abundant appreciation of other people, which found expression in kindly personal notes and in obituary tributes for the *British Medical Journal*. For many years—and up to a few months of his death—he regularly reviewed books for the *Journal*; he enjoyed doing this, and his judgment of a book was always remarkably sound.

A man so largely endowed with vital energy could not rust in retirement, and he betook himself to various fields of activity. One was the secretaryship of the British Health Resorts Association, where his special gifts of organization came into play, for he made that body do a quite remarkable work on almost no funds at all, and secured for it a place in the sun. Nothing could have been better handled than the various conferences he arranged under its auspices at different resorts. Another field he ploughed was that of the Public Medical Service, becoming secretary of the London Service and a member of the Public Medical Service Subcommittee of the B.M.A. He was also chairman of the Advisory Council of the Medical Section of British Industries House.

Cox lived long enough to see many changes at Tavistock Square. The Association which he helped to remake grew out of all recognition before he died. When he visited Headquarters, as he frequently did, there were ever fewer remaining of those who had worked with him. But those who do remain will always recall a kindly open-hearted colleague, zealous, outspoken, sympathetic, with something of the ruggedness of his native North, but always with the sympathetic undertone—a man who served his profession alike in office hours and in the night watches, who commended everywhere the Association's ideals, and who was in the eyes of many its personal embodiment.

He knew one great sorrow—the death of his wife in 1927—and in early life he endured many hardships, but he declared when he was aged 84 that he had had a happy life for which he had much to be thankful. "I can say, as few men can, that I have done just the work I wanted to do and through it have made a host of friends, among whom have been many of the salt of the earth."

An old colleague writes: Alfred Cox was the most single-minded man I have ever met. The B.M.A. was for him the centre of his existence. He followed its fortunes with the most intense interest and devotion to the end of his long life, and all this with a disinterestedness that characterized a man who put self last and the cause first. Cox had great integrity of mind and character, tempered with a human warmth of personality that endeared him to those who came to know him well. He was a great reader, and his range of interests was remarkably wide. If one recommended him a book and he did not like it, back would come a forthright and trenchant criticism of it. His great pride was in the part he played in forming the constitution of the B.M.A., and for this alone he will always have his place in the history of the Association. Cox was a "whole man" who was incapable of stooping to any meanness, and his memory will long be held in affection by those who knew him.

J. A. TORRENS, M.D., F.R.C.P.

Dr. J. A. Torrens, consulting physician to St. George's Hospital and formerly dean of the medical school, died at Haslemere on August 23 after a short illness. He was 72 years of age.

James Aubrey Torrens was born on September 4, 1881, the younger of the two sons of Mr. Henry C. Torrens, and was educated at St. Paul's School, where he won the senior scholarship and the leaving exhibition in science. Entering St. George's Hospital Medical School in October, 1899, with a scholarship in arts, he had a distinguished career as a student in the school, gaining the prize in anatomy and physiology and the Brodie Prize in surgery. He qualified M.R.C.S., L.R.C.P. in 1905 and two years later obtained the London degrees of M.B., B.S. He was elected M.R.C.P. in 1909 and proceeded to the M.D. in 1920. At St. George's he held a number of junior appointments, including those of house-surgeon and house-physician, assistant curator of the museum and medical registrar, and was elected assistant physician to the hospital in 1911. In August, 1914, he joined the R.A.M.C. and served overseas in France and Mesopotamia, with the rank of temporary major, in the first world war.

In 1921 Torrens became F.R.C.P. and was promoted to the senior staff at St. George's, where he served his full twenty years, and was elected consulting physician on his retirement. From 1922 to 1925 he was dean of the medical school, and its present prosperity is largely due to him. Among other appointments he was attached in a consulting capacity to the Chelsea Hospital for

Women and the Harrow Cottage Hospital. He also examined in medicine for the Society of Apothecaries, the London Conjoint Board, and Oxford University. Torrens married in 1910 Miss Hilda Martin. She died in 1944 and he married Miss Elizabeth Chapman in the following year, and she survives him. By his first marriage he had one daughter.

We are indebted to R. R. J. for the following appreciation: "Jim" Torrens was a good, all-round physician as well as a scholar. He was careful and conscientious in his work, popular alike with patients and colleagues, and emphatically a good man to clerk for. He took endless trouble with his clerks, and the post of his house-physicianship was eagerly sought by the newly qualified. When he began practice he took a small house in Upper Berkeley Street and moved to 46, Wimpole Street in 1920. I was one of his tenants for fifteen years in Wimpole Street and we had entered St. George's in the same year. I owe him more than I can tell for more than fifty years of friendship. I have heard that Dr. Walker, high master of St. Paul's School, was anxious to keep Torrens on the classical side; had he done so Jim would certainly have had a distinguished career at the university. But he made up his mind to enter the medical profession, and what the university lost the profession and St. George's in particular gained. Torrens was not a prolific author, but, with the late Arthur Latham, he brought out a book, *Medical Diagnosis*, and he contributed articles on medical treatment of aortic aneurysm and embolism to Latham and English's *System of Treatment*: but I think the best of his professional writing was the article on typhoid fever and paratyphoid which he contributed to the *Official History of the War*. In his younger days he was a good runner and a capital three-quarter in the hospital Rugby fifteen.

T. O. ROBSON, M.B., F.F.A. R.C.S.

Dr. T. O. Robson, formerly senior anaesthetist at Aberdeen Royal Infirmary, died on August 5 while on holiday at Ballater, Aberdeenshire. Seven years ago he underwent a serious operation, but it is only little over a year since he was compelled because of gradually failing physical powers to give up the work to which he had devoted high qualities of heart and mind for many years.

Thomas Ogilvie Robson was born at Aberdeen, one of a family of ten, on July 3, 1893, and was the son of a well-known agricultural merchant. He was educated at Aberdeen Grammar School and the University of Aberdeen, and earned distinction not only in the classroom and the hospital but also on the playing fields. Cricketers and Rugby footballers and tennis players of his time will recall his joy in the thrills of many a hard game. He was always a keen card player and he spent many happy hours playing bridge, a game in which he excelled. His medical studies were interrupted in 1914 when, as a member of Aberdeen University Officers Training Corps, he went to France with the British Red Cross Society as a dresser. He was sent home in 1915 to finish his course, and he graduated M.B., Ch.B. in 1916 and was immediately commissioned in the R.A.M.C. His next three years were spent on service, almost all the time with a field ambulance in France during the grim fighting until the end of the war.

After demobilization, he went to Ballater on Deeside as assistant to the late Dr. (later Sir) Alexander Hendry. There through happy, if sometimes hard, days in the hills, he apprenticed himself to his work as a general practitioner in medicine. Then came his return to Aberdeen in 1922, when he took over the practice of the late Dr. George M. Edmond. Even taking full account of his distinction in his specialist work in anaesthetics, it may be fairly said that Dr. Robson did his best work in general practice, where no personal or medical detail was too trivial for him and where, always, his patient was his friend.

He joined the staff of Aberdeen Royal Infirmary as assistant anaesthetist in 1924 and in 1944 became the senior anaesthetist and lecturer in anaesthetics in the university. On the inauguration of the National Health Service and the reorganization of hospital staffs he was appointed consulting anaesthetist in charge of the North-east of Scotland. He was admitted F.F.A. R.C.S. in 1952, and he retired in May last year.

Robson was a staunch church and family man. Predeceased by his wife nine years ago, he is survived by a daughter and two sons. His daughter is a doctor, and so also is his elder son, who is in practice at Potton, Bedfordshire. His younger son is a naval officer. His profession and his friends suffer a great loss in the passing of this wise, kindly, and essentially modest man.—H. F.

J. C. M. GIVEN, M.B.E., M.D., M.R.C.P.

Dr. J. C. M. Given, who died on August 10 at Tunbridge Wells, where he had been living in retirement, was a son of Liverpool. Not only was he born there—on November 22, 1867—but he was trained there in the work which he chose for his profession.

When John Cecil Mackmurdo Given began his medical studies the old Liverpool Royal Infirmary School of Medicine was in course of being transformed into a faculty of the Liverpool University College, later to attain independence as the University of Liverpool. He won the Oakshott Prize in anatomy and the Derby Scholarship in clinical medicine and surgery. Having taken the diploma of L.S.A. in 1890, he was one of a few Liverpool students who chose to present themselves for the examinations of the University of London, and, after several months of study at University College Hospital, was admitted to the degree of M.B. London in 1891. In 1894 he proceeded to the M.D. and in 1901 was elected to the Membership of the Royal College of Physicians of London. With these academic distinctions and acknowledged as one of the most highly trained and cultured students of his time, he would certainly have gained appointment to a Liverpool hospital. The opinion of his abilities held by the leading hospital men of his time, Sir William Mitchell Banks, Dr. T. R. Glynn, and Mr. F. T. Paul, was well known.

But Given chose general practice, probably because the personal relations of general practice made a special appeal to him. To some extent he hid his light under a bushel. He was not fond of public appearances or of work on committees, but those who knew him were aware of his two special interests in addition to his medical work: social affairs and anthropological research. His interest in social schemes in Liverpool was chiefly exercised through his patients, among whom he came to know many who were leaders in these affairs. His influence was chiefly active behind the scenes, but many a scheme owed much to his advice and advocacy. Yet he remained above all a doctor of medicine. One habit on which his friends sometimes rallied him was the keeping of voluminous notes on his patients so that each had a dossier which almost amounted to a life

history. Of few men could it be more truly said that he knew his patients. Another characteristic of his practice which struck his contemporaries was the exceptional use he made of the laboratories; he was in advance of his time in this respect. During the first world war he was on the staff of several Red Cross hospitals, his work there being recognized by his appointment as M.B.E. in 1920. The quality of his work in general practice, significant of a mind that was cultured as well as trained, was the chief reason for his election as president of the Liverpool Medical Institution in 1926: he was the first general practitioner to hold the post, which he filled with dignity and distinction. His presidential address was entitled "The Neanderthal Race," and his address at the opening of the 1927–8 session was entitled "Palaeopathology and Evolution." A member of the Institution from 1890 to 1935, when he left Liverpool, he served on its council in 1900–01 and again in 1928–9 and he was honorary librarian in 1911–12 and vice-president in 1921–2, in addition to being president for the 1926–7 session.

The first Annual Representative Meeting of the British Medical Association, which was held in 1903, coincided with the establishment of Divisions within the Branches of the Association. Dr. Given, who was a member of the B.M.A. for 62 years, became the first honorary secretary of the Liverpool (Southern) Division and continued in that office until 1911. Subsequently he represented the Southern Ward on the executive and ethical committees of the reorganized Liverpool Division, of which he was chairman in 1913–14. In 1935 he retired to Tunbridge Wells and became a member of the Kent Archaeological Society, taking a lively interest in its activities, and he founded and became the honorary curator of the Tunbridge Wells Museum, and a member of the Natural History Society. He also maintained his lifelong interest in social progress by becoming a member of the Council of Social Service.

J. J. ANNING, L.M.S.S.A.

Dr. J. J. Anning, a member of a well-known medical family in Leeds, died there on August 14, ten days before his 84th birthday. He was the brother of the late Dr. G. P. Anning, who died just over a year ago. James John Anning was a widower and is survived by two sons, one of whom is Dr. S. T. Anning, a specialist in dermatology, and two daughters. His eldest son, Dr. C. C. Paul Anning, chief medical adviser to the Social Services Department of the Transvaal Chamber of Mines, died in Johannesburg about three years ago.

We are indebted to Dr. WILLIAM PICKLES for the following appreciation: Judgment on the life and work of a friend is apt to be not quite impartial, and yet I feel I am not in error in considering the life of James Anning as satisfactory as a life could possibly be. He was a West Countryman by birth and was born almost 84 years ago. His mother was widowed, and financial stress at home made it impossible for him to realize his ambition of beginning his medical studies on leaving school. He therefore qualified as a pharmaceutical chemist, and I first met him running a successful business in Woodhouse Lane, Leeds, and—is it credible?—attending as much of the medical course at the Leeds School as his duties permitted, qualifying as L.S.A. with little difficulty in 1902. This was a struggle of which he spoke to me feelingly as only possible with the aid of his wife, who then and at all times loyally stood by him in all his undertakings.

Immediately on qualifying an excellent opening came his way of succeeding Dr. William Dobson at Beeston Hill, Leeds, who died while Anning was deputizing for him. With a family by then of three children he felt bound to take it, no doubt with many a longing backward glance at experience as a resident and the attainment of the Conjoint qualification, neither of which ambitions was he able to gratify. The lack of the latter, always a source of disappointment to himself, was never a serious handicap in his career, and the decision to grasp this very favourable opportunity was correct, as the sequel proved.

It was four years after this that I became associated with him and learned to like and respect him. Even so early, with an ever-increasing practice, I found he had developed that faculty, always the attribute of the successful doctor in busy town practice, of being ably swiftly to distinguish the serious from the trivial, the significant as against the merely interesting. My position as dispenser meant much more than mere dispensary work, and was akin to that of the medical apprentice of an earlier epoch. Many a time did he call me into his consulting-room, always giving me the impression that he would like my help and so giving me that confidence which means so much to young people. For this I have always been grateful to him, for his tuition in dispensing, for which his background peculiarly fitted him, and, in these days, when calligraphy is a lost art, for his example in pride of penmanship. His handwriting was not only legible but beautiful, and he retained that all his life, as a letter from him a year ago bears witness.

Besides building up one of the largest practices in Leeds he was medical officer to the Leeds Corporation Transport Department for many years and did a great deal of ambulance training for the personnel of the Midland Railway. He even found time to act as medical officer to the famous Leeds United Football Club. During the first world war he served as a captain in the R.A.M.C., mainly in hospital ships. Between the wars he was lecturer in pharmacy in the University of Leeds, twice chairman of the Leeds Division of the British Medical Association, and four times a representative at the Annual Representative Meeting. Having retired to Eastbourne in 1937, he continued to work part-time on Ministry of Health boards, but in 1940, his house being heavily bombed, he returned to Leeds and worked for the rest of the war as locum in his son's practice.

He was brought up among the Plymouth Brethren and remained a devoted member of the Meeting. His faith was a very real thing to him which he definitely carried into his daily life. His true humility, as is the case with all real doctors, was no mere pose, his conscientious attitude to his patients, be their afflictions trivial or serious, his personal and professional character of crystal honesty, must always be a gracious memory to his family and to us, his friends, and an honour to the Leeds School. I feel that to quote from the Sermon on the Mount is not inapt: "Blessed are the meek: for they shall inherit the earth."

Medico-Legal

GLOVE IN LUNG

Carrying out the operation of right lower lobectomy for chronic bronchiectasis in a 30-year-old man, a surgeon reports[1] that he found the cause of his patient's troubles to be a surgical glove which had been in the chest for twelve years. At the age of 18 the patient had had empyema as a result of pneumonia complicating measles. He was treated by rib resection and drainage. The chest wound was thereafter dressed every three or four days by a house-surgeon, and three weeks later the patient was discharged from hospital with the wound still healing. The parents continued to change the dressing, and the wound closed

[1] DeNicola, R. R., *J. Amer. med. Ass.*, 1954, 155, 1043.

over completely one month later. The patient was seen once more at the hospital.

Three years later, and for the succeeding nine years, the patient suffered increasingly from symptoms characteristic of bronchiectasis, with severe coughing spells and the production of much purulent sputum. When the chest was opened at operation dense adhesions were found between the lower lobe and the chest wall and middle lobe. In the course of dissection a large abscess filled with pus was entered, and it was from this cavity that the glove was removed. The finger-tips had been cut from it and it had evidently been used to facilitate drainage of the empyema twelve years before. The glove had apparently then been packed with gauze, which was gradually removed. At some time during this treatment the glove inadvertently dropped into the chest cavity. In spite of this mishap, healing went on to completion, and it was only later that suppuration began. The glove was removed three years ago and the patient has fully recovered his health.

Vital Statistics

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment was reported in July, 1954, was 97, compared with 119 (revised figure) in June and 117 in July, 1953.

The number of cases of industrial diseases in the United Kingdom reported during July was as follows: lead poisoning 8, aniline poisoning 1, anthrax 1, epitheliomatous ulceration 11, and chrome ulceration 14; total 35. There were no deaths.

Infectious Diseases

The chief variations in the trends of the notifications of infectious diseases in England and Wales during the week ending August 14 were increases of 380 for whooping-cough, from 1,710 to 2,090, 60 for dysentery, from 324 to 384, and 45 for acute pneumonia, from 234 to 279, and decreases of 101 for scarlet fever, from 532 to 431, and 52 for measles, from 2,892 to 2,840.

The largest rises in the incidence of whooping-cough were 48 in Durham, from 78 to 126, and 32 in Kent, from 143 to 175. The largest variations in the trends of measles were falls of 48 in Norfolk, from 112 to 64, and 35 in Yorkshire West Riding, from 224 to 189, and a rise of 33 in Staffordshire, from 38 to 71. Only small fluctuations were reported in the returns of scarlet fever. 7 cases of diphtheria, 11 fewer than in the preceding week, were notified. This is the smallest number of cases of diphtheria notified in any week.

97 cases of acute poliomyelitis were notified. These were 8 more for paralytic and 7 more for non-paralytic cases than in the preceding week. The largest returns were Essex 10 (Chigwell U.D. 4, Brightlingsea U.D. 2, Wanstead and Woodford M.B. 2), Lancashire 9 (Liverpool C.B. 4, Manchester C.B. 2), Warwickshire 7 (Birmingham C.B. 6), and Yorkshire West Riding 7 (Leeds C.B. 2, York C.B. 2).

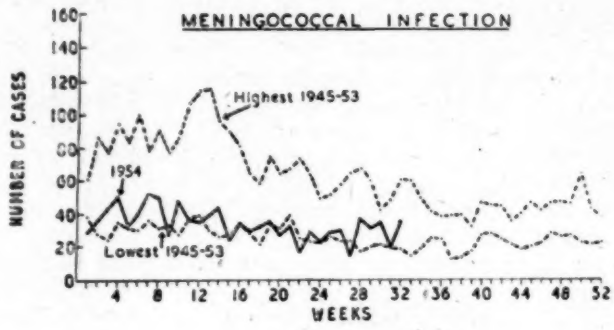
The largest returns for dysentery were London 66 (Fulham 13, Southwark 13), Lancashire 64 (Liverpool C.B. 20, Manchester C.B. 14, Salford C.B. 11), Northamptonshire 29 (Northampton C.B. 29), Yorkshire West Riding 29 (Sheffield C.B. 17), Warwickshire 18 (Birmingham C.B. 15), and Middlesex 18.

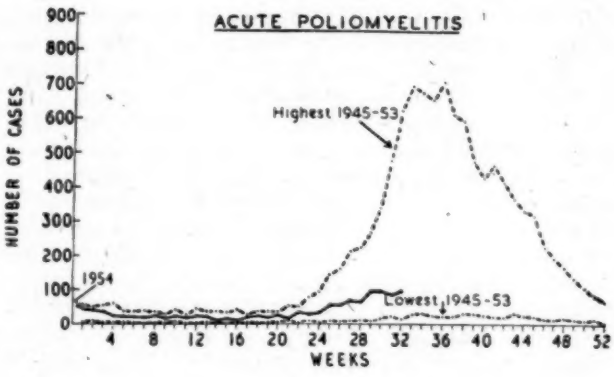
Week Ending August 21

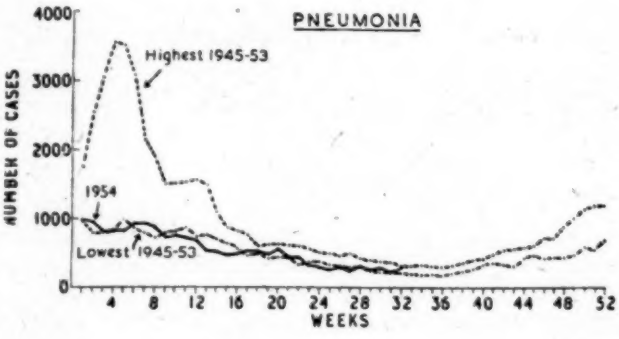
The notifications of infectious diseases in England and Wales during the week included: scarlet fever 379, whooping-cough 1,942, diphtheria 8, measles 2,255, acute pneumonia 225, acute poliomyelitis 89, dysentery 390, paratyphoid fever 21, and typhoid fever 6.

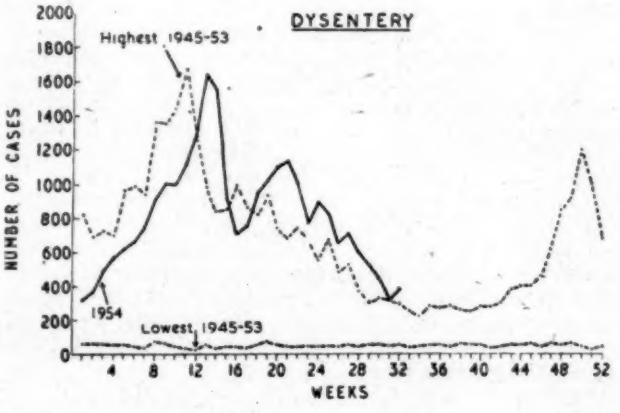
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 14** (No. 32) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	7	2	8	1	0	17	1	8	0	0
Dysentery	384	66	113	0	9	309	38	88	1	2
Encephalitis, acute	5	0	0	0		9	1	0	0	
Enteric fever:										
Typhoid	4	0	0	1		2	0	1	3	
Paratyphoid	15	3	0	0	5 (B)	11	1	0	0	1 (B)
Food-poisoning	181	20		0		516	54		7	
Infective enteritis or diarrhoea under 2 years				10	19				15	56
Measles*	2,840	123	46	87	102	4,394	65	1	120	148
Meningococcal infection	35	1	7	3	1	20	3	12	0	2
Ophthalmia neonatorum	26	1	3	0		45	4	0	1	
Pneumonia†	279	11	71	2	0	239	26	133	2	
Poliomyelitis, acute:										
Paralytic	60	2	22	4	3	151	19	9	8	11
Non-paralytic	37	2				115	17			
Puerperal fever§	252	31	18	1		259	41	5	0	
Scarlet fever	431	24	69	11	19	1,037	58	113	17	51
Tuberculosis:										
Respiratory	670	61	88	21				129	28	
Non-respiratory	104	11	9	7				18	3	
Whooping-cough	2,090	92	134	10	45	4,357	389	320	70	76

DEATHS in Great Towns	1954					1953				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		0			0		0			1
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	3	0	1	10	2	1	0	0
Influenza	3	0	1	0	0	3	0	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	1		
Pneumonia	122	22	14	8	5	119	13	10	3	6
Poliomyelitis, acute	1	0			0	8	2			0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	81	8	6	0	4	89	7	8	1	5
Non-respiratory		2	7	0	0		2	10	0	0
Whooping-cough	5	1	2	0	0	2	0	0	0	0
Deaths 0–1 year	168	20	24	8	13	223	31	24	2	14
Deaths (excluding stillbirths)	4,312	584	476	97	149	4,240	614	513	75	150
LIVE BIRTHS	7,803	1157	907	219	378	7,675	1145	967	239	372
STILLBIRTHS	166	19	20			186	29	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New C.M.O. for Ulster.—Dr. F. F. MAIN, senior administrative medical officer of the Scottish Eastern Regional Hospital Board, has been appointed chief medical officer to the Northern Ireland Ministry of Health and Local Government, in succession to Dr. JAMES BOYD, who is shortly retiring. Dr. Main graduated at Edinburgh in 1927. After experience in the public health department there he was appointed deputy M.O.H., Kilmarnock. In 1937 he went to Perth as M.O.H., where he remained until 1948, when he became S.A.M.O. of the Scottish Eastern Regional Hospital Board. Dr. Main is a past president of the Perth Branch of the B.M.A.

Committee on Homosexuality and Prostitution.—The Home Secretary and the Secretary of State for Scotland have announced the names of the fourteen members of the committee which is to inquire into the laws relating to homosexual offences and prostitution. The chairman is Mr. J. F. WOLFENDEN, Vice-Chancellor of Reading University (see *Journal*, July 17, p. 182). There are three doctors: Dr. DESMOND CURRAN, senior psychiatrist at St. George's Hospital and civilian consultant in psychological medicine to the Royal Navy; Lady STOPFORD, who is also a magistrate and the wife of Sir JOHN STOPFORD, the Vice-Chancellor of Manchester University; and Dr. JOSEPH WHITBY, a general practitioner in North London and formerly an assistant physician at the Maudsley Hospital. The other members of the committee are the Regius Professor of Moral and Pastoral Theology at Oxford, a Minister of the Church of Scotland, the Principal of the University College of Wales at Aberystwyth, the chairman of the London County Council, the Recorder of Oxford, a former Procurator-Fiscal at Glasgow (Mr. JAMES ADAIR), Lord LOTHIAN, two Members of Parliament (Sir HUGH LINSTEAD and Mr. W. T. WELLS), the chairman of the Scottish Association of Girls' Clubs (Mrs. MARY COHEN), and the chairman of Uxbridge juvenile courts (Mrs. KATHLEEN LOVIBOND).

Control of Mosquitoes.—The Ministry of Health has issued a revised edition of the *Memorandum on Measures for the Control of Mosquito Nuisances in Great Britain* (H.M.S.O., price 1s. 3d. net). The revision, which particularly concerns the use of modern insecticides, has been carried out by Sir GORDON COVELL and Mr. P. G. SHUTE, of the Malaria Reference Laboratory, Horton Hospital, Epsom. The memorandum describes the varieties of mosquitoes found in Britain, as well as outlining measures for their control.

Lasker Award.—Lord NUFFIELD is to receive the Albert Lasker Award, a silver statuette of the winged victory of Samothrace and a thousand dollars, for his "outstanding achievement in the development of services for the physically disabled." This was announced this week by the International Society for the Welfare of Cripples and the Albert and Mary Lasker Foundation. The presentation will be made at The Hague on September 15.

Registers of Medical Auxiliaries.—Recently issued national registers of medical auxiliaries, published by the Board of Registration, include the registers of chiropodists, operating theatre technicians, and orthoptists. Each contains the names, addresses, and qualifications of the auxiliaries concerned. Copies of the registers are available free to doctors, hospitals, and official bodies on application to the Registrar, Board of Registration of Medical Auxiliaries, B.M.A. House, Tavistock Square, London, W.C.1.

Psychiatric Institute in India.—The first Indian Institute of Mental Health was officially opened in Bangalore (Southern India) on August 7 by the Indian Minister of Health, RAJKUMARI AMRIT KAUR. It is intended as a post-graduate teaching and research centre for psychiatry,

affiliated to Mysore University. The director is Dr. M. V. GOVINDASWAMY. The institute was initiated by the World Health Organization, when two years ago Dr. W. MAYER-GROSS, of the Crichton Royal, Dumfries, went to India to plan the project. W.H.O. apparently intends to finance some of the teaching staff.

"Family Doctor."—The September issue contains a special school section, opening with an article by Sir ALLEN DALEY on schools "then and now." The other articles in the section are on the first term at grammar school, play centres, infections (by Professor W. GAISFORD), drinks for thirsty children, school uniforms, and parent-teachers' associations. Elsewhere in the issue there are notes on poliomyelitis and hormone creams. Attention is drawn to the Braille edition of *Family Doctor*, price 1s. 6d.

COMING EVENTS

American College of Gastroenterology.—First annual convention (nineteenth annual convention of the National Gastroenterological Association) at The Shoreham, Washington, D.C., October 25 to 27. Details from National Gastroenterological Association, 33, West 60th Street, New York, 23.

Royal Sanitary Institute.—Birmingham sessional meeting on "The General Practitioner and Local Authority Personal Health Services," on October 21, at 10 a.m. in the Council Chamber.

Silicosis and Occupational Chest Disease.—Conference sponsored jointly by the McIntyre Research Foundation of Toronto and the Saranac Laboratory, from February 7 to 9, 1955, at Saranac Lake, New York. Details from Norman R. Sturgis, jun., Saranac Laboratory, Saranac Lake, New York.

Heberden Oration.—Dr. ROBERT M. STECHER, of Cleveland, Ohio, will deliver this year's oration at the Postgraduate Medical School of London on September 24 at 5 p.m. His subject will be "Heberden's Nodes." Members of the medical profession are cordially invited to attend.

London Medical Exhibition.—At Royal Horticultural Hall, Westminster, S.W.1, from September 15 to 19. Tickets from British and Colonial Druggist Ltd., 194, Bishopsgate, London, E.C.2.

International College of Surgeons.—Twentieth anniversary congress in Geneva, May 23 to 26, 1955. Details from Congress Secretariat, 6–8, rue de la Confédération, Geneva.

The Benjamin Ward Richardson Lecture will be delivered by Sir ARTHUR MACNALTY at the Royal Sanitary Institute, London, on December 8, at 2.30 p.m. He will speak on "The Work of Benjamin Ward Richardson; its Effect on Modern Public Health Practice."

London School of Hygiene and Tropical Medicine Association.—The School Association Dinner will be held this year at the Holborn Restaurant, London, W.C.1, on Friday, October 22, at 6.45 for 7.30 p.m. Each member may bring one guest, and there will be dancing after dinner. Tickets (25s. each) can be obtained from Miss K. M. Shaw, M.B.E., London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C.1.

St. Thomas's Hospital Old Students' Dinner will take place in the New Hall, at the Royal College of Surgeons, Lincoln's Inn Fields, on October 7, at 7 for 7.30 p.m. Sir MAX PAGE will be in the chair. Tickets, price 30s. (exclusive of drinks), can be obtained from the honorary secretary.

NEW ISSUES

Abstracts of World Medicine.—The August issue (Vol. 16, No. 2), which is now available, contains abstracts of important papers drawn from medical and other scientific journals published in some 20 different countries and in all five continents. The subjects covered range over the whole field of clinical medicine and include pathology, bacteriology, pharmacology, and chemotherapy; there are also sections dealing with medical genetics, public health and industrial medicine, forensic medicine and toxicology, anaesthetics, radiology, and the history of medicine.

Issued monthly; annual subscription £4 4s., single copy 8s. 6d.; a specimen will be sent free on request.

British Journal of Venereal Diseases.—The new issue (Vol. 30, No. 3) will be available in a week's time. The contents include:

SEROLOGY OF SYPHILIS BASED ON RECENT OBSERVATIONS. Reuben L. Kahn.
CONCENTRATION OF THE CELL SUSPENSION IN THE WASSERMANN TEST. P. N. Coleman.
STUDIES ON THE TREPONEMAL IMMOBILIZATION TEST. A. E. Wilkinson.
SOME REFLECTIONS ON THE TRICHOMONAS VAGINALIS. Neville Mascall.
LABORATORY ASPECTS OF TRICHOMONAS VAGINALIS. F. Lanceley.
LABORATORY ASPECTS OF TRICHOMONAS INFECTIONS. M. G. McEntegart.
BRITISH FEDERATION AGAINST THE VENEREAL DISEASES. C. S. Nicol.

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APPOINTMENTS

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MACDOUGALL, I. A., M.B.E., M.R.C.S., L.R.C.P., D.P.H., County Medical Officer of Health and Principal School Medical Officer, Hampshire County Council

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BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Gardner.—On August 19, 1954, at Queen Charlotte's Maternity Hospital, London, W., to Joyce (formerly Grose), wife of Dr. P. S. Gardner, of 28, Watchfield, Sutton Court Road, Chiswick, W., a son—David Ian.

Taylor.—On August 10, 1954, at Maternity Hospital, Mill Road, Cambridge, to Regina, wife of Dr K. A. Taylor, of Christ's College, Cambridge, and the Gold Coast, a son—Kobine.

DEATHS

Aldis.—On August 21, 1954, at Guildford, Surrey, Carlyle Aldis, M.B., B.S.

Barker.—On August 16, 1954, at the Henry Gauvain Clinic, Alton, Hants, Frederic Barker, M.B., B.S., late of Kobe, Japan, and Parkstone, Dorset.

Bottomley.—On August 21, 1954, Francis Carr Bottomley, O.B.E., M.D., of 1, Beechwood Avenue, Boscombe, Bournemouth.

Bowyer.—On August 16, 1954, Harold Wilson Bowyer, M.D., of 829, Chorley Old Road, Bolton, Lancs.

Crisp.—On August 25, 1954, George Bedford Crisp, M.R.C.S., L.R.C.P., Lieutenant-Colonel, R.A.M.C., retired.

Ellison.—On August 21, 1954, at St. Bartholomew's Hospital, London, E.C., Hubert Henry Lacey Ellison, M.R.C.S., L.R.C.P.

Fisher.—On August 16, 1954, at "Postmead," Portesham, Dorset, Joseph William Fisher, Ph.D., M.R.C.S., L.R.C.P., aged 53.

Greene.—On August 1, 1954, Henry Bertram Blodwell Green, M.R.C.S., L.R.C.P., of 17, Valencia Road, West Worthing, Sussex aged 90.

Greig.—On August 24, 1954, at his home, Keri Keri, Bay of Islands, New Zealand, James Alexander Greig, F.R.C.S.Ed., formerly Medical Missionary at Kirin, Manchuria.

McGuinness.—On August 18, 1954, at Sunderland Hospital, Joseph William Alison Montgomery McGuinness, L.R.C.P.&S.Ed., L.R.F.P.S., of 5, Harrison Road, Edinburgh.

Taylor.—On August 15, 1954, at Deaconess Hospital, Edinburgh, Herbert Francis Lechmere Taylor, M.D., D.P.H., of 11, Tantallon Place, Edinburgh.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Pregnancy and Air Travel

Q.—*Are there any contraindications to a healthy pregnant woman flying to South Africa? Are any special precautions advised?*

A.—There are no contraindications to a healthy pregnant woman flying to South Africa, provided the journey is made in a pressurized aircraft and completed before the end of the eighth month. Travel in a pressurized cabin is necessary to safeguard against anoxia, the cabin atmosphere being maintained at the equivalent of that of an altitude of 8,000 ft. (2,400 m.) or less. The limit of eight months is set to avoid delivery taking place in flight, as well it may any time in the ninth month, especially in multiparae. Precautions are to regulate the bowels and diet so as to avoid abdominal distension; to move about as little as possible in the aircraft, so as to minimize oxygen requirements; if liable to morning or travel sickness, to take an anti-airsickness tablet (hyoscine hydrobromide, gr. 1/100—0.65 mg.) half an hour before flight; and to ensure that any seat belts used on take-off, landing, or during turbulent conditions do not press unduly on the abdomen. If an airline is informed that a pregnant woman is to be a passenger, she will be accommodated in an aft-facing seat, so that the seat belt need be only loosely applied and then placed low down in the region of the groins. In addition, an oxygen set is placed on board in case it is needed.

Male Infertility

Q.—*A patient of mine is being investigated for infertility. His sperm count was 15 million per ml., with poor morphology and motility. What further investigations are indicated? What treatment is recommended? What is the prognosis?*

A.—The first step in further investigation is to have two more seminal analyses, making sure that the specimen jar is warmed slightly before it receives the seminal fluid. Marked variation from one specimen to another is not uncommon. If the findings are confirmed and the patient presents no obvious abnormalities, it is doubtful if other investigations will be of much help. Testicular biopsy may have a prognostic value; if it shows a few normal tubules, surrounded by a majority in which the germinal epithelium is grossly degenerate, clearly no treatment can be of value; but if it shows a more uniform picture of hypospermatogenesis, the chances of therapeutic success are greater. Determination of 17-ketosteroids is not likely to help, but a B.M.R. estimation may be useful if hypothyroidism is suspected. Our ignorance of the cause of most instances of oligospermia means that all treatment is empirical. Three main types have been used: (1) Gonadotrophins for direct stimulation have rarely been successful and are not recommended. (2) (2) Testosterone in large doses—for example, testosterone propionate 100 mg. intramuscularly thrice weekly or testosterone phenyl propionate 100 mg. weekly for two or three months—to depress spermatogenesis is the method of Heckel *et al.*;[1,2] on cessation of treatment it is claimed that a rebound effect occurs, carrying the sperm count to levels far above that found before treatment. This rebound does undoubtedly occur sometimes, and over the course of many months after cessation of treatment; but it is missing from many patients treated in this way. (3) Testosterone in moderate dosage—for example, three 100 mg. pellets—by implantation.[3] This presumably has a directly stimulating effect and may prove successful in perhaps 50 to 60% of cases. The prognosis for such a patient as that described is not too bad, provided his wife is fertile. Even without any improvement from treatment he might well succeed in begetting a child, and there is a better than even chance that one form of treatment or another may improve the seminal fluid and so increase his chances of parenthood.

REFERENCES

1. *J. Clin. Endocrinol.*, 1951, **11**, 235.
2. *Fertil. and Steril.*, 1952, **3**, 49.
3. Swyer, G. I. M. (1953). *British Medical Journal*, **2**, 1080.

Ultra-violet Light as a Tonic

Q.—*(a) Is ultra-violet light considered of benefit to children who are debilitated with complaints other than respiratory? One recollects articles in various journals where controlled experiments did not prove any benefit with ultra-violet light, but an appreciable number of consultants still order it, and parents state that benefit has been received. (b) Before this treatment, is it necessary to have an x-ray of the chest when there is no symptom? If so, does this apply to all ages?*

A.—(*a*) Although many investigations have been made into the tonic effects of ultra-violet irradiation, no scientific proof has ever been forthcoming that these rays have any immunizing or protective effect. The matter was thoroughly investigated by the Medical Research Council, with negative results. On the other hand, it is an impressive form of treatment and can lead to a pleasant pigmentation of the skin, which no doubt has a psychological effect. (*b*) As exposure to ultra-violet irradiation can lead to the activation of a pulmonary tuberculous focus, it is the counsel of perfection to radiograph the chest before exposure, at all ages. But in the absence of symptoms this is seldom done, and no series of disasters has been reported.

Interstitial Emphysema

Q.—*In cases of interstitial emphysema the air is capable of disappearing very rapidly from the tissues. The textbooks refer to its being absorbed. I would like to know whether this absorption is into the capillaries, or via the lymphatics. If into the capillaries, what is the mechanism whereby the nitrogen enters the plasma? If absorbed in the gaseous state, do the minute air bubbles become disintegrated in the pulmonary capillaries?*

A.—The question infers some special activity of the capillaries or lymphatics in the absorption of gas from bubbles in the tissues. This is not the case. All such gas is absorbed by diffusion into and solution in the surrounding tissues. The gaseous tensions or concentrations in these tissues are kept almost constant by a dynamic equilibrium between metabolic gas exchange and diffusion of gases between capillaries and tissues. Fluid and lymph circulation will contribute to this equilibrium to a very slight extent. When air enters the tissues the oxygen tension in the bubbles will be about 150 mm. Hg., whereas the oxygen tension in the tissues will be about 40 mm. Hg.; thus oxygen will diffuse into the surrounding tissues and be used in metabolic processes. Carbon dioxide will diffuse from the tissues, where the average tension is 46 mm. Hg., into the air bubble. As more oxygen is lost than carbon dioxide gained the bubble will decrease in size, remaining at atmospheric pressure. Thus the concentration of nitrogen in the bubble will rise above the level in the tissues (about 583 mm. Hg.) and nitrogen will then diffuse into the tissues. Such diffusion will again cause reduction in the size of the bubble and the oxygen and carbon dioxide tensions in the bubble will rise above the tissue tensions, and these gases will therefore diffuse back into the tissues. These changes do not occur in distinct stages but are, of course, a continuous process. The essence of this rather complicated situation is that the absorption of any particular gas from the bubble will cause it to become smaller and raise the tensions of the other gases in the bubble above the level in the tissues. It is obvious that this is an unstable situation and that it will continue until the bubble disappears. With regard to the inquiry concerning entry of small bubbles into the circulation, this will occur only in very special circumstances.

There must be damage and opening of blood vessels, and the entry of gas into the vessels is usually assisted by the pumping action of continuing intra-thoracic pressure changes. As the commonest site of entry is into damaged lung capillaries or venules the intravascular bubbles usually cause systemic aero-embolism. If bubbles are introduced experimentally (animals) or accidentally into systemic veins then these usually lodge in the lungs. However, in animal experiments some bubbles of a surprising size can apparently pass the pulmonary capillary mesh, and it is thought that there may be some vascular short circuit of the lungs in such cases. If air or any other gas is introduced in very large quantities into systemic veins then froth will occur in the ventricles and the pumping action of the heart will be lost, with fatal circulatory insufficiency.

Intolerance to Plastic Contact Lenses

Q.—*Is there any advantage in having contact lenses of glass rather than plastic? A man of 40 has been wearing plastic contact lenses for four years, and is now having recurrent conjunctivitis which is relieved only by removing the lenses. Could this be due to a sensitivity to the plastic, or is some other cause more likely?*

A.—During recent years plastic has increasingly been replacing glass in the making of contact lenses. Some of the patients develop an intolerance to the wearing of these appliances, whatever the material employed and however great the skill of the fitter. If this patient's difficulty is due to plastic as such, then probably tests by an experienced allergist would demonstrate his susceptibility—in which case it would be worth his while to try glass contact lenses. If no idiosyncrasy were revealed by such tests, one would have to advise him to abandon contact lenses altogether.

Ephedrine and Disseminated Sclerosis

Q.—*A colleague of mine, whose wife has disseminated sclerosis of many years' standing, with asthma, tells me that when ephedrine is given for her asthmatic attacks the spasticity of her legs is greatly relieved. I remember a similar effect in a case of mine many years ago. Is this well known?*

A.—The action of ephedrine in reducing spasticity is not recognized, nor is there any scientific reason why it should produce this effect.

NOTES AND COMMENTS

Inheritance of Deaf-mutism.—Dr. A. BERNSTEIN (Department of Genetics, Wisconsin University, U.S.A.) writes: Although the information given by the questioner in his inquiry about deaf-mutism ("Any Questions?" July 10, p. 110) is rather sparse, it does make one question the opinion given by your expert. Deaf-mutism is generally agreed to be caused by a recessive autosomal gene, possibly by more than one acting in concert. On the evidence before us here, however, this hypothesis does not appear to meet the facts. Each of three males but none of seven females display the disease, thus strongly suggesting some form of sex-linkage or other form of sex-determination. Assuming a sex-linked recessive gene, then one is faced with a picture analogous to that obtaining in haemophilia—that is, without other evidence as to the patient's genotype, there is a 25% probability of deaf-mute sons of the marriage with an apparently normal male. This is a much higher chance than the postulated random congenital defects. It is interesting, moreover, to note that all of the three brothers are deaf-mutes. The number is small, but allied to the preponderance of females (7:3) one wonders whether this might indicate an undue male mortality, possibly among those zygotes not carrying the gene for deaf-mutism—that is, that the mother carries a "lethal" on the second member of the X-chromosome pair. This is highly hypothetical and one could wish for far more extensive information about other members of the family, their pregnancies, and whether there was a high incidence of miscarriages. In other circumstances one might agree with the philosophy contained in your expert's final sentence, but not when the likelihood of diseased sons is as high as 25%.

OUR EXPERT writes: Dr. Bernstein is, of course, right in calling attention to the peculiar association between sex and abnormality in this sibship. When the question was received further information was sought from the inquirer, who lives abroad. He was asked to confirm that the sibship consisted of seven girls, all normal, and three boys, all affected, and that the family histories of both the man and the girl were otherwise negative so far as could be determined. He was also asked how many boys were included in the sibship of the girl's mother and of her mother's mother. No reply was received and, through an editorial error, a provisional answer went forward for publication without two qualifications, which were certainly desirable—namely, that it was assumed that the history as given was accurate, and, secondly, that sex-linkage was considered and set aside as very unlikely. The probability of getting such an extreme association between sex and abnormality, if in fact they are independent, is 1/120, which is a distinctly low figure. If, however, the condition were sex-linked in this family, the findings would be well within ordinary limits of expectation. This is the evidence in favour of sex-linkage. On the other hand there is, so far as I am aware, no suggestion in the literature that hereditary deaf-mutism (or hereditary congenital deafness, to use Dr. Fisch's preferable term—see *British Medical Journal*, July 31, p. 341) is ever sex-linked. Incidentally, the literature includes some extensive and carefully analysed bodies of data; for example, the fine study of Lindenov ("The Aetiology of Deaf-mutism," *Opera ex Domo Biologiae Hereditariae Humanae Universitatis Hafniensis*, vol. 8. Copenhagen, Munksgaard, 1945). It seems to me, therefore, that the evidence against sex-linkage is so strong that we should need a much lower probability than 1/120 before accepting sex-linkage rather than chance as the explanation for an apparent association with sex in a particular sibship. Faced with the problem of answering the question put by the girl, and making the assumptions about the family history already mentioned, I should have no hesitation in basing the answer on straight recessive transmission and in assuring her that the chance that a child of hers will be affected is very small. But I do agree with Dr. Bernstein that a full explanation should have been given in the published answer and also that the family would be well worth detailed study, if this were possible.

Myxomatosis.—In reply to a further inquiry about myxomatosis (see "Any Questions?" July 31, p. 313), on the risk of domestic animals becoming infected, OUR EXPERT writes: You will find that in an article by Sir Charles Martin published in the 4th Report of the Director, Institute of Animal Pathology, Cambridge, in 1934, page 32, there is a table giving a list of the animals which under experimental conditions have not been found to be susceptible to myxomatosis. They are listed as follows: fowl, pigeons, duck, man, monkey, cattle, horse, sheep, goat, cat, dog, mouse, rat, guinea-pig, and hamster. Since that date other experiments have been carried out with similar results. In regard to the rabbit, susceptibility seems to be confined to the genus *Oryctolagus* to which wild rabbits in Europe and Australia belong. The indigenous rabbits of America belong to another genus, *Sylvilagus*, and are more closely allied to hares. They are resistant to the virus. The general view is that the hare is not susceptible, although three natural cases have been reported during the recent outbreak in France. There is some doubt, however, about whether these were true hares.

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